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Improving the Synthesis of Fragrance Ingredients

*A thesis submitted for the degree of
Doctor of Philosophy*



*By
James S. Sharley*

*Under the supervision of
Prof. Ian R. Baxendale*

21/12/2016

Declaration

The work described in this thesis was carried out in the Department of Chemistry at Durham University between October 2013 and December 2016, under the supervision of Prof. Ian Baxendale. The material contained has not been previously submitted for a degree at this or any other university. The research reported within this thesis has been conducted by the author unless indicated otherwise.

Abstract

The synthesis of three fragrance ingredients currently manufactured at International Flavours and Fragrances (IFF), Benicarló, Spain are primarily investigated herein. After reviewing the literature surrounding each of these, efforts were made to improve upon their current synthesis through the development of new methodology. Assessments of the compatibility of the developed chemistry, as well as other industrially important transformations, with continuous flow processing were also made.

Hedione (methyl dihydrojasmonate) was the subject of the first of these three projects. Efforts were focused towards novel dehydrohedione (DHH) syntheses from Hedione. A new copper(II) bromide mediated oxidation was firstly developed that was shown to be capable of oxidising the Hedione enol-acetate to DHH in high yield. The methodology was also applied to a range of other substrates including to the synthesis of a phenol. A catalytic system was also developed and demonstrated on a model substrate derived from desoxyanisoin. A second novel DHH synthesis was achieved by direct Hedione oxidation *via* an α -chloro intermediate which underwent spontaneous elimination in methanol. Of the chlorinating agents used, sulfuryl chloride was found to be the best, giving DHH yields of 77%, an improvement upon the 71% yield associated with the currently used three-step process. The process was found to be easily scalable and its amenability to flow was demonstrated.

The second project involved an assessment of a Diels-Alder reaction currently used by IFF for the synthesis of Isofloriffone, a precursor to δ -Damascone. The reaction is currently catalysed using AlCl_3 in high loading and an alternative catalytic system was sought. While none of the alternative methods employed gave yields that came close to those achieved with AlCl_3 , key factors influencing the yield were identified as the AlCl_3 loading and the temperature, which must be kept low enough to prevent a runaway/diene polymerisation. The Lewis acid catalysed

reaction, as it stands is not suited to flow, however, it is proposed that many thermal Diels-Alder processes in the flavour and fragrance industry would benefit from continuous flow manufacturing protocols.

The final project involved the synthesis of α -dehydroherbac, a precursor to a fragrance ingredient known as Galbascone. The current process used by IFF gives rise to a mixture of products and was poorly understood prior to this work. Following mechanistic studies, a proposed overall mechanistic pathway for the reaction was outlined that accounted for the products formed and their ratios. Following this, two novel routes towards the desired α -dehydroherbac isomer were investigated. The first of these failed to give the desired product but revealed unprecedented conjugate addition reactivity of a Wittig reagent. The second route developed made use of an irregular nitro-aldol reaction followed by a Nef reaction. High selectivity towards the desired isomer was successfully achieved through steric control of an imine intermediate. The resultant process, offered both an improved yield (51% vs 38% both over two steps) and selectivity (84% vs 50% isomeric purity) over the process used currently and was demonstrated for a range of substrates.

In summary, three new reactions were discovered; an irregular conjugate addition reaction of a Wittig reagent, a catalytic and non-catalytic CuBr_2 mediated oxidation of ketones and enol acetates and a one-pot chlorination-elimination oxidation process which is well suited to flow and currently being trialled at pilot plant scale at IFF Benicarló. Key features of the Isofloriffone and α -dehydroherbac industrial processes were also established and a new process based on known chemistry was developed that resulted in higher yields and selectivities than the currently used α -dehydroherbac synthesis.

Acknowledgements

I would firstly like to thank Ian Baxendale for this opportunity and for the continued academic support and guidance throughout my time in Durham. My thanks also go to our industrial collaborators as well as the research group and its members, many of whom have become good friends. In particular, I am indebted to Marcus Baumann, Paolo Filipponi, Christian Stanetty, Carl Mallia and Laurens Brocken for their help and for the training I received, especially during my first year. My thanks also go to the above, as well as Johnathan Bliss, Dan Clapham, Te Hu, Teppo Leino, Matteo Bergami, Lukas Englert, Seger van Millighem, Fabien Deplante, Alex Nicholls, Rohan Vase and of course, Emily Cardew and our families for their friendship, support and for keeping me level-headed throughout my studies. I must also acknowledge the support of the chemistry department's NMR and mass spec technical staff as well as the relevant non-technical staff.

Abbreviations

Ac	acetate
AIBN	azobisisobutyronitrile
ASAP	atmospheric solid analysis probe
bn	billion
b.p.	boiling point
BPR	back pressure regulator
Bu	butyl
^t Bu	tertiary butyl
°C	degrees centigrade
COSY	homonuclear correlation spectroscopy
CSTR	continuous stir tank reactor
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	<i>N,N</i> -diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DoE	design of experiments
EtOAc	ethyl acetate
EtOH	ethanol
EI	electron ionisation
ESI	electrospray ionisation
FT-IR	fourier transform infrared spectroscopy
GC-MS	gas chromatography – mass spectrometry
g	gram
kg	kilogram
h	hours
HMBC	heteronuclear-multiple bond correlation spectroscopy
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear-single bond correlation spectroscopy
Hz	Hertz

IFF	International Flavors and Fragrances
IL	ionic liquid
<i>J</i>	coupling constant
L	litre
mL	millilitre
LC-MS	liquid chromatography – mass spectrometry
LUMO	lowest unoccupied molecular orbital
M	molar
m.p.	melting point
MeOH	methanol
MeCN	acetonitrile
min	minutes
mol	moles
mmol	millimoles
Ms	methanesulfonyl
MW	microwave
NMR	nuclear magnetic resonance spectroscopy
NOESY	nuclear overhauser effect spectroscopy
PPA	polyphosphoric acid
ppm	parts per million
ppb	parts per billion
<i>i</i> Pr	isopropyl
psi	pounds per square inch
PTFE	polytetrafluoroethylene
r.t.	room temperature
RBF	round-bottom flask
R _t	retention time
SFC	solvent free conditions
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	toluenesulfonyl
<i>p</i> -TSA	<i>para</i> -toluenesulfonic acid

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1. Introduction

1.1. Fragrance Chemistry and the Flavour and Fragrance Industry

Since the earliest documented use of fragrances in ancient Egypt and Mesopotamia to current times, the human race has always been fascinated by scents. The first recorded production of a synthetic aroma chemical was at the Berlin Academy in 1759.¹ By the 20th century, an explosion of synthetic fragrance discoveries had occurred and we now possess the knowledge of hundreds of different fragrance structures. Natural fragrances are generally derived from terpene skeletons (Figure 1), these are built up in nature through the combination of multiple isoprene **4** units *via* processes mediated by pyrophosphate intermediates. Terpene skeletons are also observed in many synthetic fragrances, however, these exhibit a wider structural diversity beyond functionality accessible to nature (Figure 2), with the inclusion of moieties such as phenyl systems, for example. The modern-day fragrance chemist has available an extensive library of both natural and synthetic compounds capable of delivering a wide spectrum of scent notes to consumers. The full spectrum of known fragrance notes was described in 1983 by Michael Edwards in his eponymous ‘fragrance wheel’ (Figure 3),² this is still used today as a system for the categorisation of fragrances.

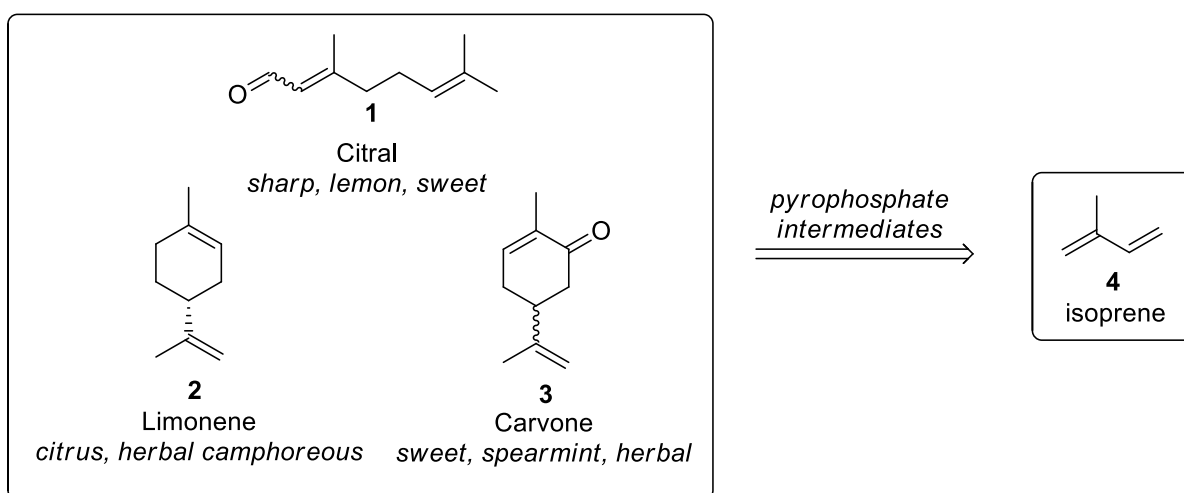


Figure 1: Natural terpenoids commonly used to impart fragrance notes.

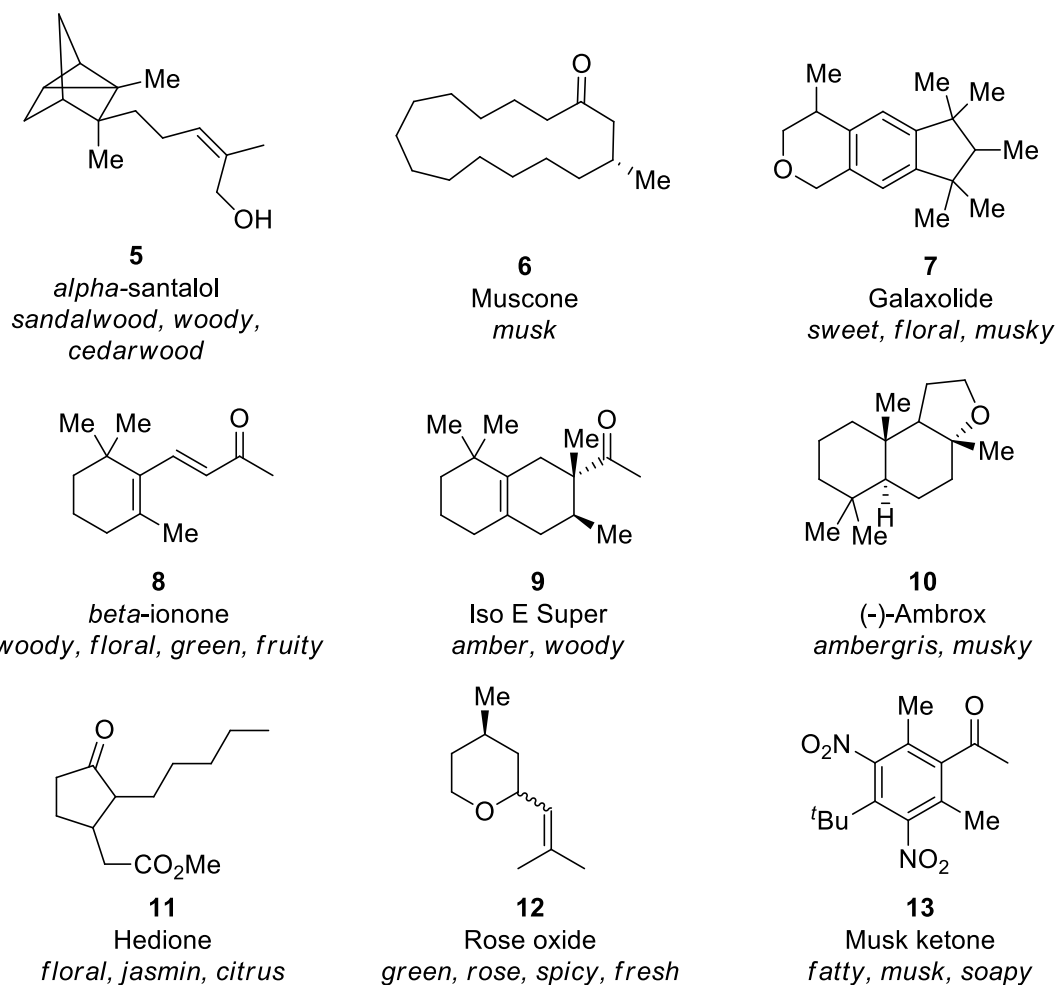


Figure 2: Some common fragrance ingredients obtained synthetically.

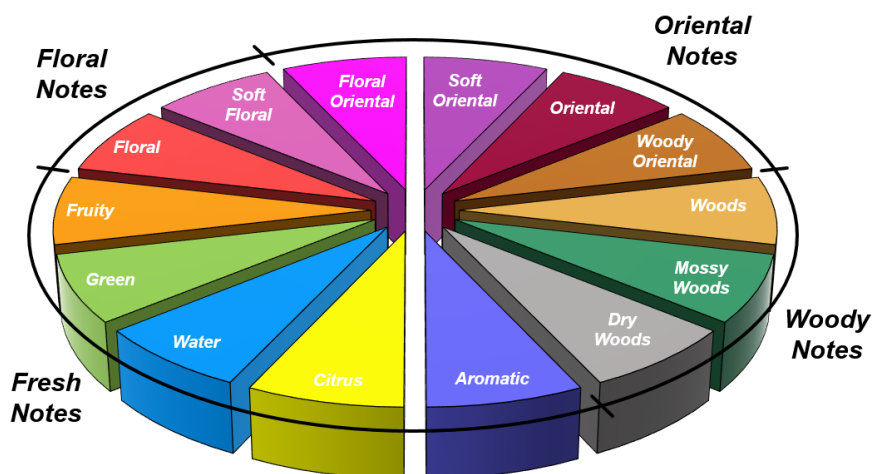


Figure 3: The Michael Edwards fragrance wheel.²

With estimated sales of over \$24 billion in 2015³ the flavour and fragrance industry represents a significant, valuable market within chemical production and analysis shows a general equal split in sales between the fragrance and flavour sector.³ While naturals will always represent an important class of flavour and fragrance ingredients, the majority of fragrance molecules produced are synthetic (ca. 560 synthetics vs. ca. 50 naturals produced at IFF's manufacturing plant in Benicarló, Spain). Synthetic flavour and fragrance production represents a multi-billion dollar outlet for synthetic organic chemistry, an arena in which chemists are constantly striving to deliver cheaper and more environmentally friendly processes. Indeed, there is fierce competition between companies to produce at the lowest possible cost. With steady, reliable market drivers i.e. consumer demand, efforts directed towards production cost-reduction are constant and ongoing within all flavour and fragrance (F&F) manufacturers.

All commercially available products comprising F&F ingredients can be traced back to innovation within bulk F&F companies as their manufactured products (both natural and synthetic) are supplied onwards to companies further down the supply chain for final product formulation. For fragrance ingredients, such formulations include fine fragrances, cosmetics, toiletries, soaps, detergents and air fresheners as well as others (Figure 4). For flavours, the major market resides in the beverages industry, with dairy, confectionary, bakery and savoury/convenience foods also representing significant outlets (Figure 5). International fragrance companies are solely responsible for the discovery, creation, process development and manufacturing of synthetic fragrance ingredients. These areas represent individually active research topics within the field of fragrances today.

The flavour and fragrance industry is generally conservative with regards to manufacturing approaches with many currently used processes still based on classical methodology from old patents. Despite trade secrets remaining closely guarded, signs of F&F companies beginning to adopt more contemporary synthetic strategies are beginning to emerge. In 2014, Firmenich

launched Clearwood, the first fragrance ingredient produced using biotechnology platforms.⁴ This year Firmenich also began producing Ambrox **10** through an enzymatic process.⁵⁻⁶ This innovation is in part driven by the potential for cost reduction that comes with such synthesis approaches and also by the current pressure to deliver ‘greener’ chemical processes.

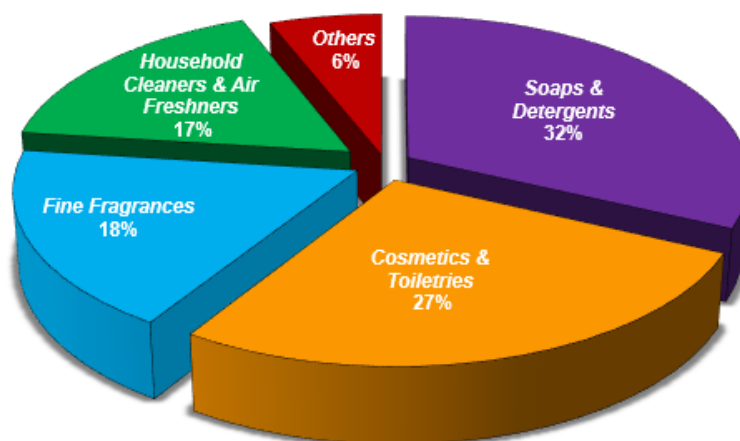


Figure 4: The global market for fragrances in 2013.³

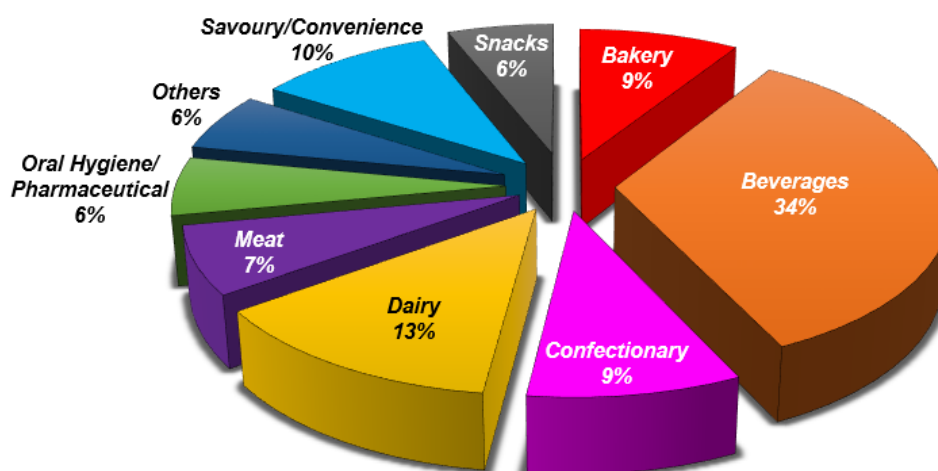


Figure 5: The global market for flavours in 2013.³

One area of innovation in chemical manufacturing is flow chemistry. Pharmaceutical companies such as Vertex, GSK, Novartis and Johnson & Johnson are currently investing tens of millions of dollars in dedicated continuous flow manufacturing facilities and R&D geared towards flow chemistry.⁷ Such endeavours require large amounts of capital investment and it will surely only be a matter of time before similar investments are seen across more of the

chemical manufacturing industry. However, the fact that the F&F industry is less lucrative than industries such as pharma must be acknowledged (2015 global sales; Pharma ~ \$1,000 bn, Agrochemicals ~ \$200 bn, F&F ~ \$25 bn).³ This is attributable to the relative low value of F&F products compared to products such as pharmaceuticals and the fact that F&F manufacturers generally act as intermediates between raw chemical suppliers and consumer goods companies leading to a much lower profit margin on products sold. Furthermore, many F&F products are manufactured on an *ad-hoc* basis and the majority of batch reactors used are ‘non-dedicated’ i.e. used for a variety of reaction types. It is therefore understandable that the confidence necessary to invest heavily in innovative manufacturing techniques and adoption of continuous manufacturing may take longer to realise for F&F companies and in many instances the construction of dedicated manufacturing facilities may simply not be economically worthwhile. There is, however, significant scope for cost reduction within manufacturing in the F&F industry through the adoption of continuous flow synthetic approaches.

1.2. Flow Chemistry

Society is rapidly moving towards a future with increasing levels of automation, particularly with regards to manufacturing. More and more labour-intensive jobs classically performed by humans are being performed robotically. Implications for automation in manufacturing are being realised across many areas⁸ and the previously mentioned pharmaceutical companies are currently investing large amounts of capital in continuous manufacturing facilities.⁷ Advantages with regards to increased automation are obvious, with large potential for cost reduction, space saving and improved health and safety implications. Flow chemistry and more generally, continuous manufacturing, go hand-in-hand with automation and the fact that the

implementation of continuous flow technology can also give rise to improved synthetic procedures is well known.⁹⁻¹³

A basic depiction of batch vs. flow for a multi-step synthesis is shown in Figure 6. In batch-mode multiple reaction vessels are required with intermediate work-ups (and purifications). A flow-setup allows for ‘telescoping’ between steps/reactors as shown in Figure 6, making it amenable to further downstream inlets and processing.

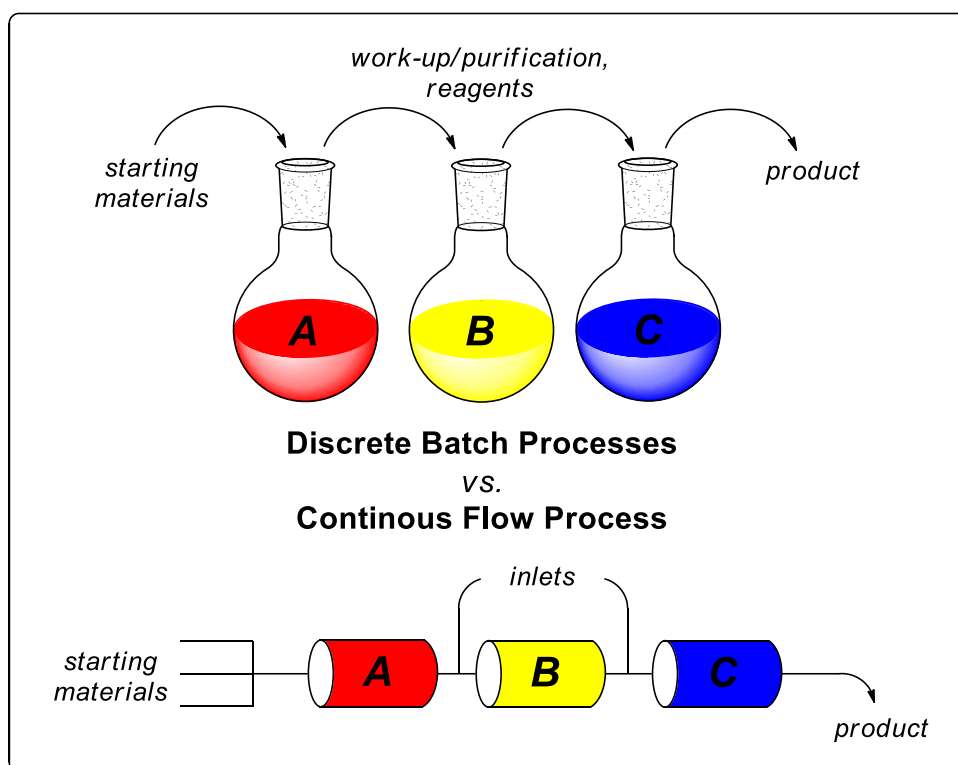


Figure 6: Batch vs. flow.

Reasons for the adoption of flow chemistry into both industry and academia¹⁴⁻¹⁸ are many (Table 1): Increased levels of automation, inherent health and safety implications due to containment, the implicit higher heat and mass transfer rates, higher temperature and pressure range access, the potential for in-line purification, monitoring and telescoping, linear scalability and more efficient mixing.

Table 1: Flow approach advantages and disadvantages.

<i>Advantages</i>	<i>Disadvantages</i>
<ul style="list-style-type: none"> • Increased levels of automation • High heat (surface-to-volume ratio) and mass transfer rates • Potential for in-line purification and telescoping • Improved compatibility with “forbidden chemistries”^a • Efficient mixing • Linear scalability and high throughput • Health and safety implications • Facile access to high temperatures and pressures 	<ul style="list-style-type: none"> • Quenching/work-up issues • Dilution effects of additional downstream flow streams • Solvent limitations for multi-step procedures • Inability to compensate for reaction kinetics • Start-up and shut-down procedures • Issues with heterogeneity

^a Chemistry deemed to be too hazardous to be carried out in batch.

Table 2: The 12 principles of green chemistry and green engineering with colour indicating the relevance of flow chemistry (major implications, minor implications, not applicable).

	Green Chemistry Principle	Green Engineering Principle
1	Prevent Waste	Inherent Rather Than Circumstantial
2	Atom Economy	Prevention Instead of Treatment
3	Less Hazardous Chemical Syntheses	Design for Separation
4	Design Benign Chemicals	Maximize Efficiency
5	Benign Solvents and Auxiliaries	Output-Pulled Versus Input-Pushed
6	Design for Energy Efficiency	Conserve Complexity
7	Use of Renewable Feedstocks	Durability Rather Than Immortality
8	Reduce Derivatives	Meet Need, Minimize Excess
9	Catalysis (vs. Stoichiometric)	Minimize Material Diversity
10	Design for Degradation	Integrate Material and Energy Flows
11	Real-Time Analysis for Pollution Prevention	Design for Commercial "Afterlife"
12	Inherently Benign Chemistry for Accident Prevention	Renewable Rather Than Depleting

There are certain drawbacks to using a flow-approach that must also be acknowledged (Table 1). Problems may arise due to quenching requirements, the necessity for solvent switching, concentration limitations, compensating for reaction kinetics over multiple steps, potential requirements for intermediate purification and issues arising due to heterogeneity. Hence, a batch approach often offers a more convenient and easier synthetic setup. Efforts directed towards addressing these drawbacks currently account for a large proportion of the research being conducted within flow chemistry.¹⁹⁻²⁴ Table 1 lists the advantages and disadvantages of a flow approach.

The 12 principles of green chemistry (Table 2) were introduced in 1998 by Paul Anastas and John Warner²⁵ and outline what is meant by and to be expected of a green chemical, process or product. Principles for which flow chemistry may be especially pertinent are highlighted as green in Table 2, for others only minor implications can be imagined.²⁶ Later, in 2003 Anastas went on to publish the 12 principles of green engineering,²⁷ the relevance of continuous manufacturing to these is also displayed in Table 2. Together these outline the compatibility of the flow approach with regards to a sustainable chemical manufacturing future.

While flow does not always prevail as the most appropriate approach, there are numerous examples within the literature where flow has been demonstrated to give superior results to batch with regards to higher yields, rates of reaction and greater selectivities.²⁸⁻³⁰ Flavours and fragrances (typically liquid or derived from liquid precursors) are particularly well suited to flow and there is a large scope for improvement upon a range of reactions currently used as industry processes by adopting flow chemistry.³¹ Flow chemistry now represents a powerful tool for the pharmaceutical industry both in a research and manufacturing capacity³² and in the years to come there will be increasing adoption of continuous flow processes across the chemical industry.

1.3. Molecules of Interest

Three fragrance molecules are primarily investigated herein, section 2 is therefore divided into three sections accordingly. The background and aims associated with each molecule/project are described in the following introductory sections (1.3.1. – 1.3.3.).

1.3.1. Hedione

In 1958, shortly after methyl jasmonate **15** was found to be a component of naturally occurring jasmine, Hedione, or methyl dihydrojasmonate **14** was discovered by Eduoard Demole of Firmenich. Methyl jasmonate was, at the time, difficult and expensive to produce and so methyl dihydrojasmonate was introduced as a synthetically viable equivalent. It was then launched as a fragrance product by Firmenich in 1962 under the trade name Hedione (derived from the Greek word ‘*hedone*’, meaning pleasure).³³⁻³⁵ The compound’s use in “*Eau Sauvage*“ by Dior in 1966 boosted its reputation as an important perfumery ingredient and it is still recognised by perfumers today as the ‘quintessence of florals with citrus’.

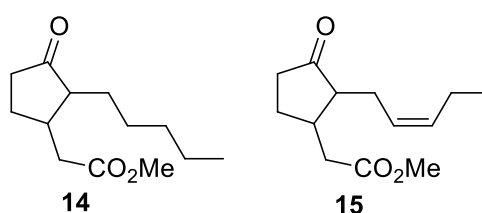
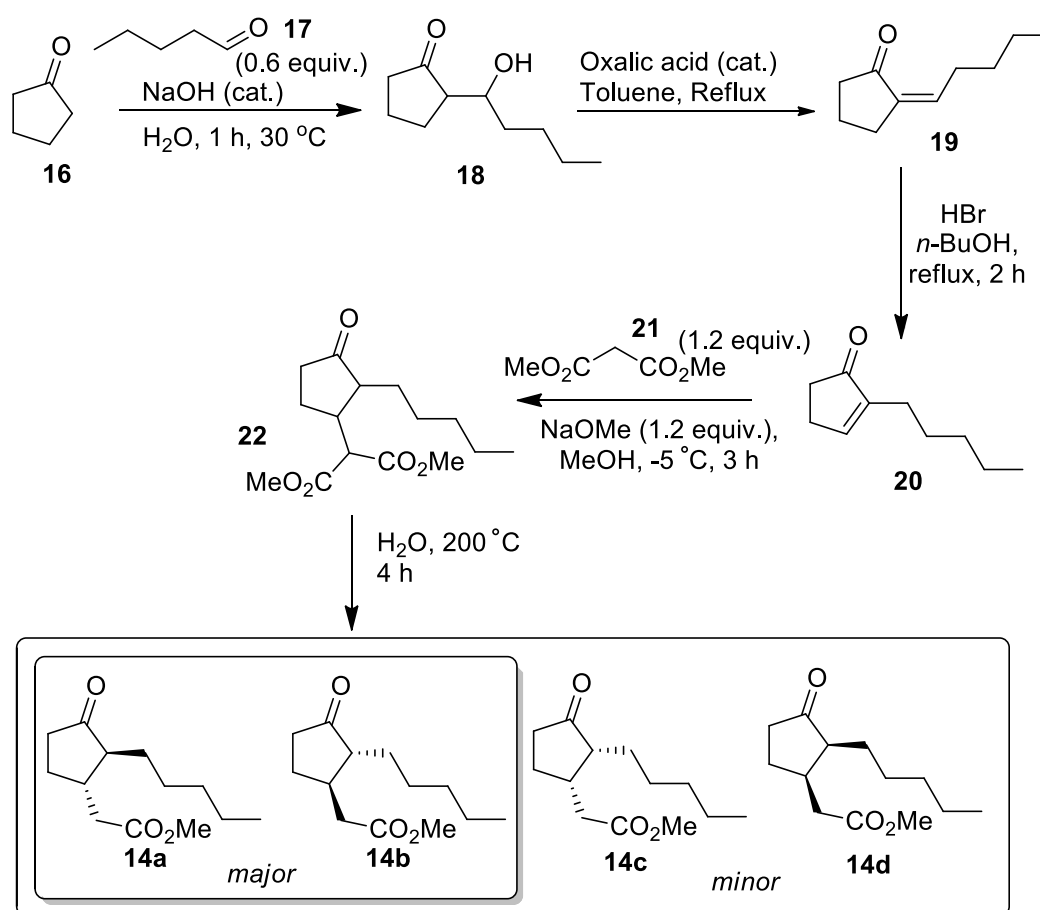


Figure 7: Methyl dihydrojasmonate **14** and methyl jasmonate **15** structures.

Following the industrialisation of nylon 6-6 synthesis throughout the 1930s and the resulting increased availability of adipic acid, cyclopentanone derived targets became increasingly accessible. Cyclopentanone **16** is prepared commercially by pyrolysis of the barium or calcium salt of adipic acid and can be easily functionalised by simple aldol condensations with aldehydes. The resultant 2-alkylidenecyclopentanones **19** themselves possess interesting jasmine-like odours, however, their direct use in fragrances was brought to a halt following the

elucidation of their skin sensitisation properties.³⁶ An aldol reaction between cyclopentanone and pentanal is the first step of the industrial synthesis of Hedione (Scheme 1).³⁷⁻³⁸ The dehydrated aldol product **19** is then isomerised to the *endo*-double bond isomer and reacted in a Michael fashion with dimethyl malonate, giving **22**. Upon heating with the gradual addition of water, decarboxylation occurs giving the monoester product **14**.³⁷ Alternatively, the decarboxylation may be carried out in a two-step process *via* initial saponification-decarboxylation followed by esterification.³⁸ The industrial route towards methyl dihydrojasmonate has remained relatively unchanged since its initial development and the fragrance ingredient is now produced at greater than 1,000 tonnes per year.³⁹



Scheme 1: An industrial route towards Hedione.

This synthesis yields predominantly the *trans* methyl dihydrojasmonate diastereoisomer, hence Hedione is sold as a mixture of 10% *cis*, 90% *trans* by Firmenich.³⁵ The relative olfactory activity associated with the *cis*-isomers, however, far exceeds that of their *trans*-counterparts.

Interestingly, higher biological activities have also been attributed to the *cis*-isomers of the jasmonate family.^{40,41}

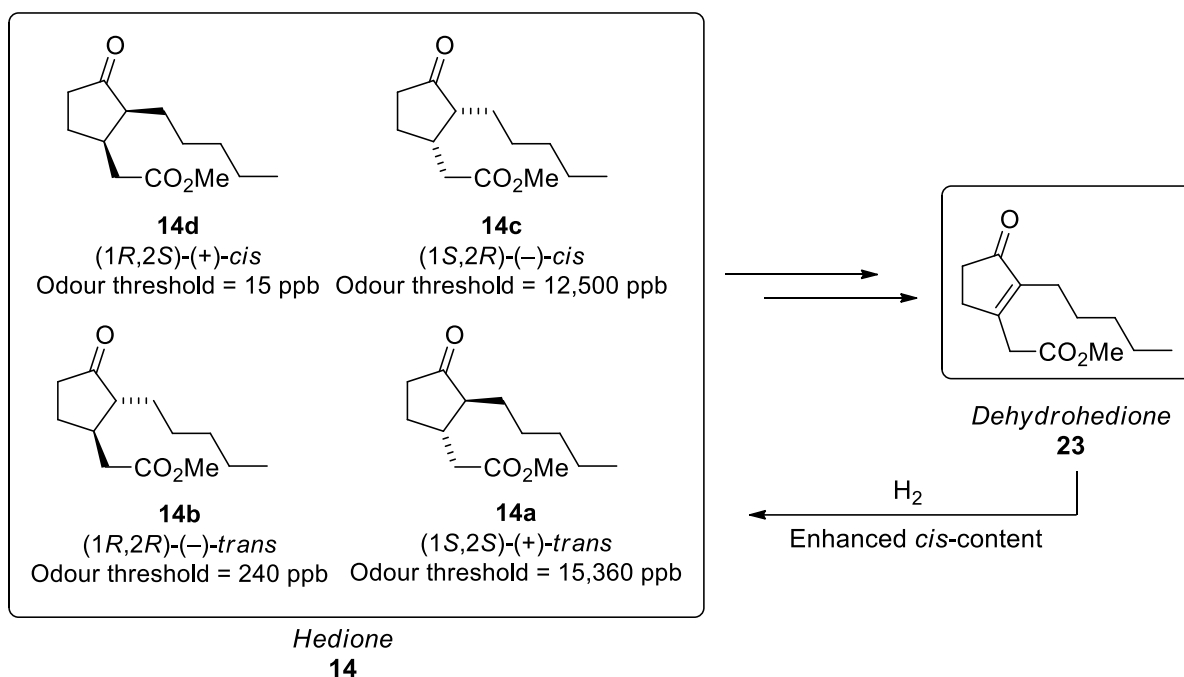
Each of the Hedione isomers are reported to possess subtly different aromas but with vastly different odour detection thresholds. Of the *trans*-enantiomers, the (1*R*,2*R*)-(–)-isomer (**14b**) has a basic floral, sweet, jasmine like odour while the (1*S*,2*S*)-(+)-isomer (**14a**) has more of a fatty, hay-like character with notes of tea/lemon peel. For the *cis*-enantiomer pairing, the (1*S*,2*R*)-(–)-isomer (**14c**) has a herbal, fatty and tea/tobacco scent while the highly desirable (1*R*,2*S*)-(+)-isomer (**14d**) is noted for its intensely floral, extremely long lasting jasmine aroma. This, coupled with its very low odour threshold (over 3 orders of magnitude lower than that of the (1*S*,2*S*)-(+)-isomer (**14a**)) makes it almost solely responsible for the Hedione scent.⁴² Hence, improving the *cis:trans* ratio would result in a compound composition with an improved scent profile.

Table 3: Different commercially available methyl dihydrojasmonate products and their *cis*-content.

Product	<i>cis:trans</i> ratio
Hedione (Firmenich)	ca. 10:90
Cepionate (Zeon)	ca. 30:70
Kharismal (IFF)	ca. 60:40
Super Cepionate (Zeon)	ca. 70:30
Jasmodione (Takasago)	ca. 70:30
Kharismal Super (IFF)	ca. 72:28
Hedione HC (Firmenich)	ca. 75:25
Hedione VHC (Firmenich)	ca. 90:10
Paradisone (Firmenich)	ca. 94:6

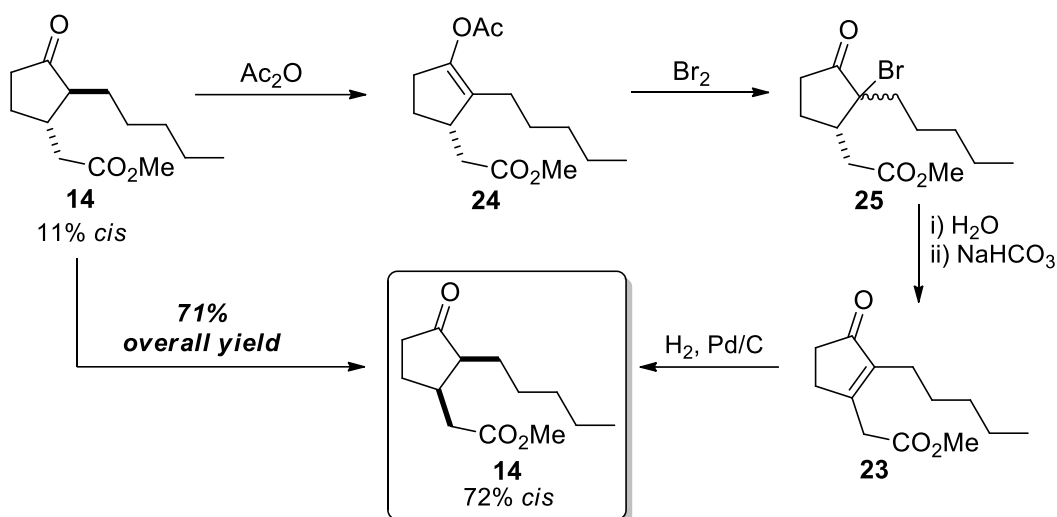
There are several products commercially available with differing *cis:trans* ratios as manufacturers use different techniques to prepare the ‘*cis*-enhanced’ material (Table 3). *Cis*-

enhancement is generally performed through hydrogenation of the α,β -unsaturated Hedione analogue, dehydrohedione **23** (DHH), (Scheme 2) making DHH a highly valuable synthetic target.



Scheme 2: *Cis*-enhancement of Hedione through DHH hydrogenation.

While multiple synthetic routes towards DHH have been developed for use at small scale,⁴³⁻⁴⁴ DHH is generally prepared at large scale via oxidation of Hedione. The current route used by IFF is shown in Scheme 3. The route comprises three steps and gives DHH in 71% yield from Hedione. DHH is then converted to ‘Kharismal’ or ‘Kharismal Super’ (see Table 3) by hydrogenation over Palladium on carbon. This route requires elemental bromine, due to the toxicity and environmental implications associated with this reagent alternative approaches are highly sought after. The aims of this project were therefore to develop new routes towards DHH that avoided elemental bromine which offered improved yields upon the current process (71%) and also to develop a flow process for the synthesis of DHH from Hedione.



Scheme 3: IFF's DHH synthesis and *cis*-enhancement strategy.

1.3.2 δ -Damascone

Damascones **26**, and their closely related structural isomers the ionones **27**, form part of an important and well-established aroma family known as the rose ketones. As natural contributors to the fragrance of a broad range of essential oils such as rose oil, they are found in nature as a result of carotenoid degradation.⁴⁵

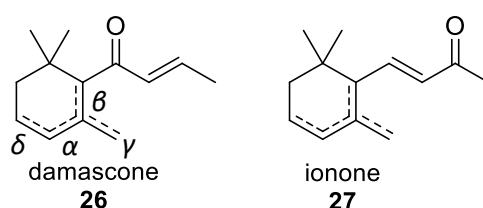
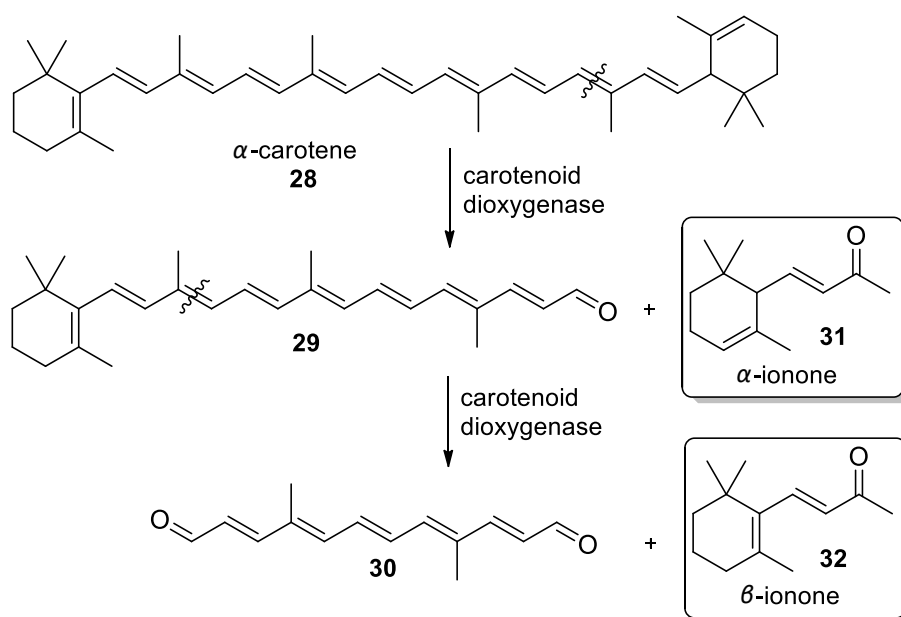


Figure 8: Ionone and damascone structures and double bond isomers.

An example of how ionones may form as a result of the break-down of α -carotene **28** by carotenoid dioxygenase enzymes is shown in Scheme 4.⁴⁶



Scheme 4: Natural ionone synthesis from α -carotene degradation.

Ionones are the perfumer's molecule of choice when a sweet or 'powdery' aroma is desired and despite their discovery in 1893 by Krüger and Tiemann,⁴⁷ α/β -ionone **31/32** were not identified in nature until almost a century later. The pioneering work that led to the conception of these fragrance ingredients also inspired the synthesis of a wide variety of additional rose ketone derivatives.⁴⁸ β -Damascone **33**, the first recorded damascone, was discovered in 1967 by researchers at Firmenich during work on the identification of the constituents of Bulgarian rose oil, *Rosa damascena*, from which this class of compound's name is derived.⁴⁹ Data concerning its structure elucidation were published in the Journal of Chromatography some twenty years later.⁵⁰⁻⁵¹

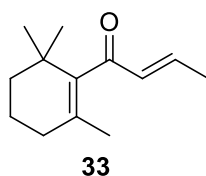


Figure 9: β -Damascone

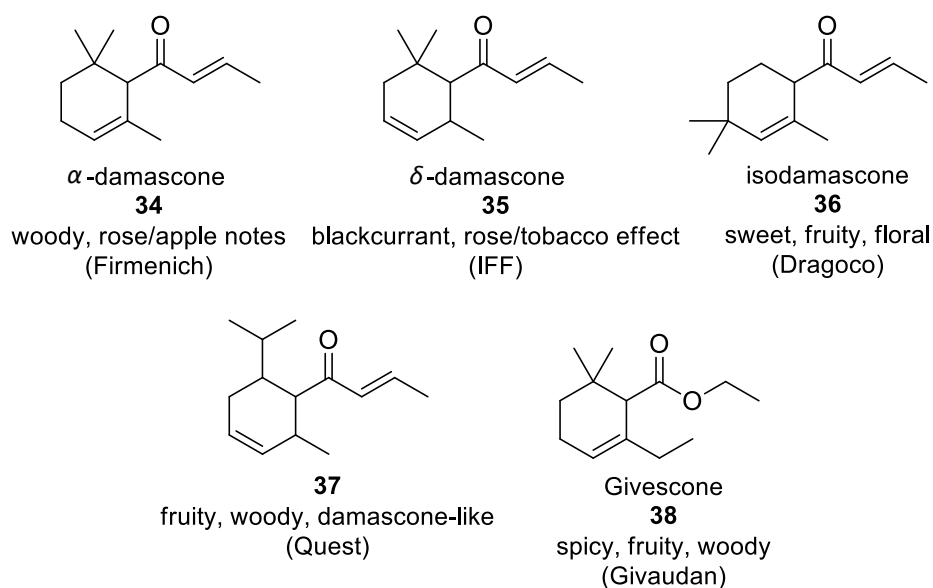
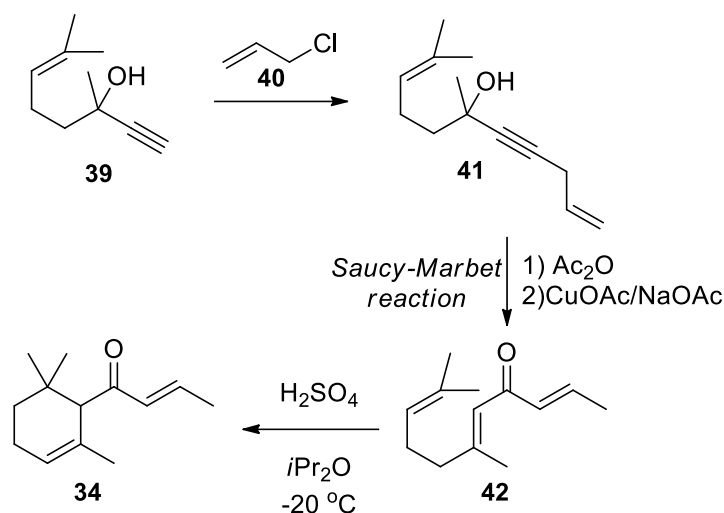


Figure 10: Commercially available damascone derivatives.

Damascones are renowned for their fruity, woody aromas and are commonly used alongside other ingredients to impart an intensifying effect. While their use is restricted to just 0.1 vol.% in perfumes due to their suspected sensitizing properties,⁵² they are still found in a wide range of products and represent a significant category of synthetic fragrance ingredients. The first industrial scale synthesis of α -damascone **34** was developed in 1970 and started from the acyclic monoterpene **39**⁵³ (manufactured from 6-methyl-5-hepten-2-one and acetylene),⁵⁴ the 4-step procedure is shown in Scheme 5.

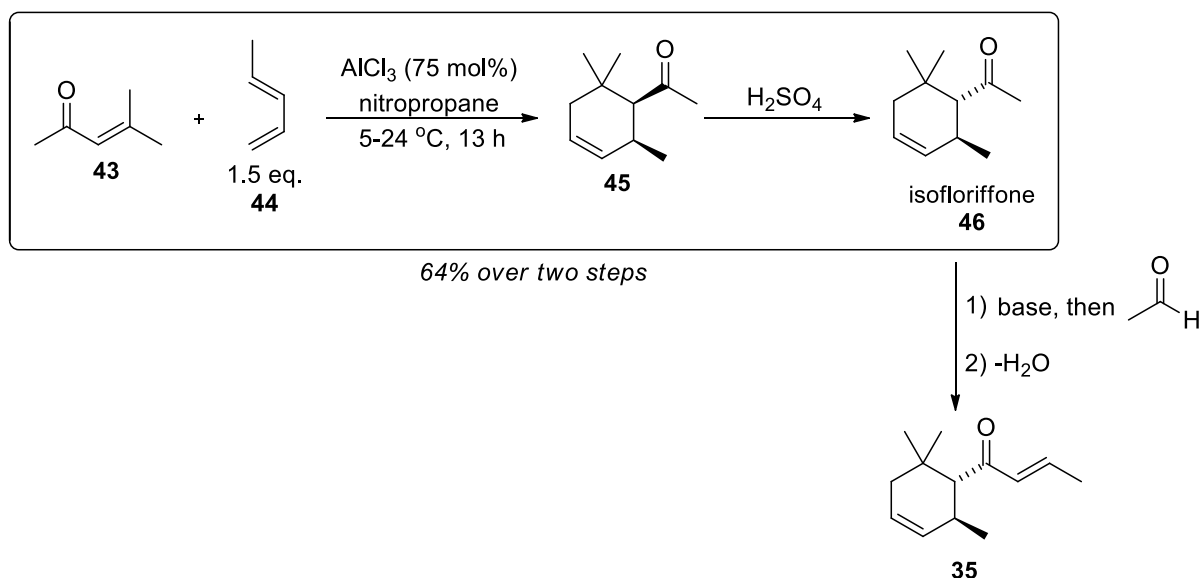


Scheme 5: An early synthesis of α -damascone.

The industrial preparation of the corresponding δ -damascone **35** used by IFF is shown in Scheme 6. The Diels-Alder (DA) reaction of mesityl oxide **43** with piperylene **44** was first reported in 1969 by chemists in Azerbaijan⁵⁵ with the full synthesis of δ -damascone being reported in 1973 by Ayyar *et al.* while investigating the synthesis of β -damascenone and its related compounds.⁵⁶ The current route has remained effectively unchanged ever since. The initial DA reaction gives the intermediate, Isofloriffone **46**, which itself possesses an interesting woody aroma but is not a commercially sold product. The DA reaction yields the *cis*-isomer **45** which is then epimerised to the *trans*-isomer **46** under acidic conditions during work-up. An aldol condensation of **46** with acetaldehyde yields δ -damascone **35**.

The reaction is a suprafacial [4+2] cycloaddition between the HOMO of the diene and the LUMO of the dienophile.⁵⁷⁻⁵⁸ Difficulties arise with the work-up due to the presence of large amounts of aluminium salts and the formation of polymeric material (due to piperylene self-polymerisation⁵⁶). Aluminium trichloride is necessary to lower the LUMO of the dienophile so that the reaction can occur. An alternate catalytic system that is both cost-effective and gives comparable yields has not yet been discovered. The main aim of the project was to investigate

the possibility of improving the yield and cost effectiveness of the reaction through alternative catalytic approaches with the goal of achieving a continuous flow process.



Scheme 6: IFF's current δ -damascone manufacturing route.

1.3.3. Galbascone

Galbascone (IFF) or Dynascone (Firmenich) **47**, (Figure 11), sometimes also referred to as green ketone, represents a synthetic fragrance ingredient with a powerful fresh, green odour. Its discovery occurred quite by accident in 1972 when it was found as a side product in the early synthesis of α -damascone **34**.⁵⁹ The compound was subsequently isolated and its structure elucidated in the following year, the name galbascone was given due to its odour's similarity with that of galbanum oil.

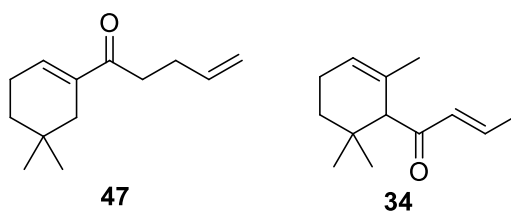
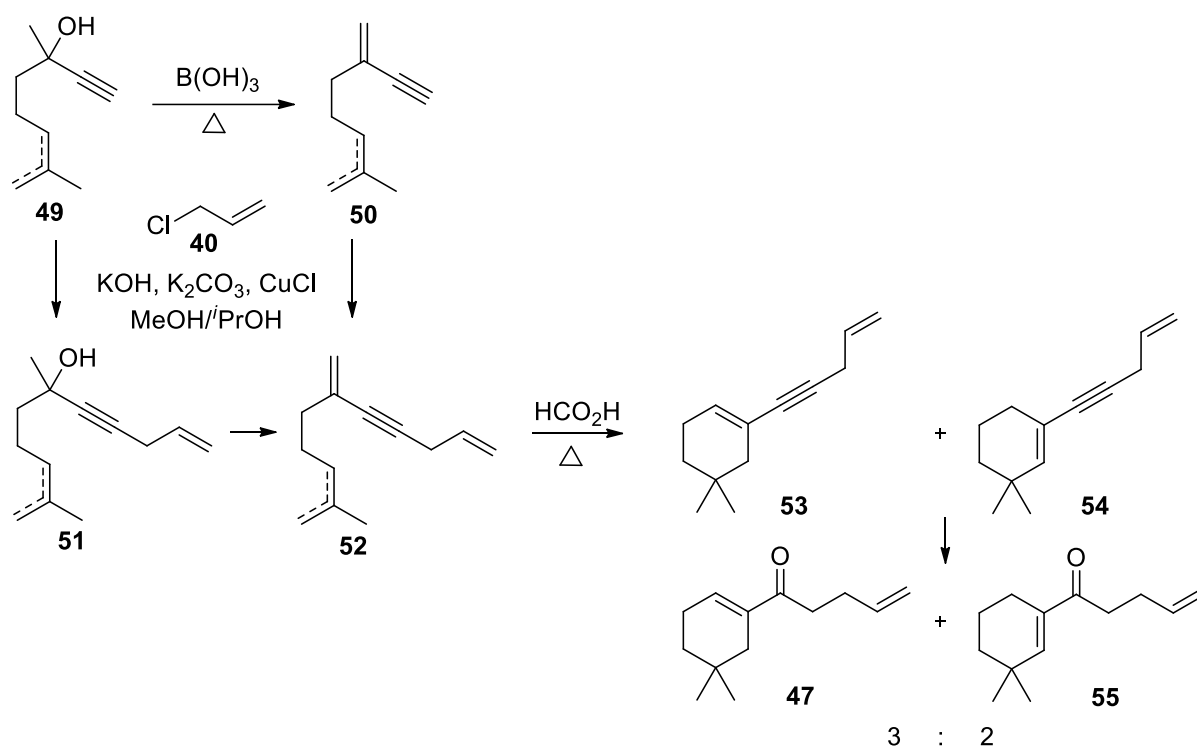


Figure 11: The structures of galbascone **47** and α -damascone **34**.

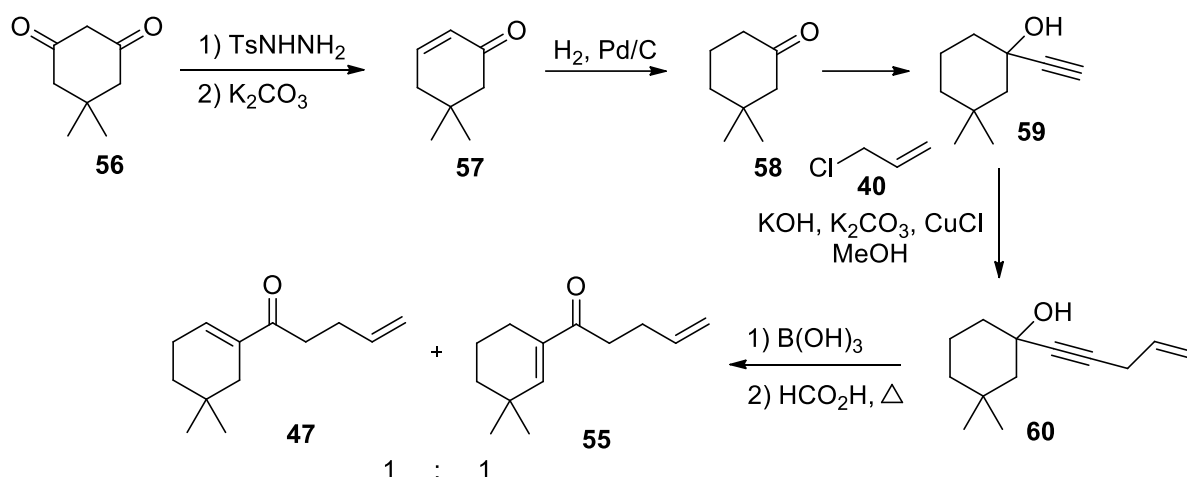
Investigations into a feasible industrial synthesis of galbascone then began and in 1976 several synthetic routes were disclosed in a patent by Firmenich.⁶⁰



Scheme 7: An early galbascone synthesis reported by Firmenich.

One synthesis started from a mixture of α/β -dehydrolinalool **49** and after dehydration, allylation, cyclisation and hydrolysis of the resultant cyclic acetylene gave a mixture of two galbascone double bond isomers, α -galbascone **47** and β -galbascone **55** in a 3:2 ratio respectively (Scheme 7). The α -isomer **47** possesses the desired scent and so is the desired product.

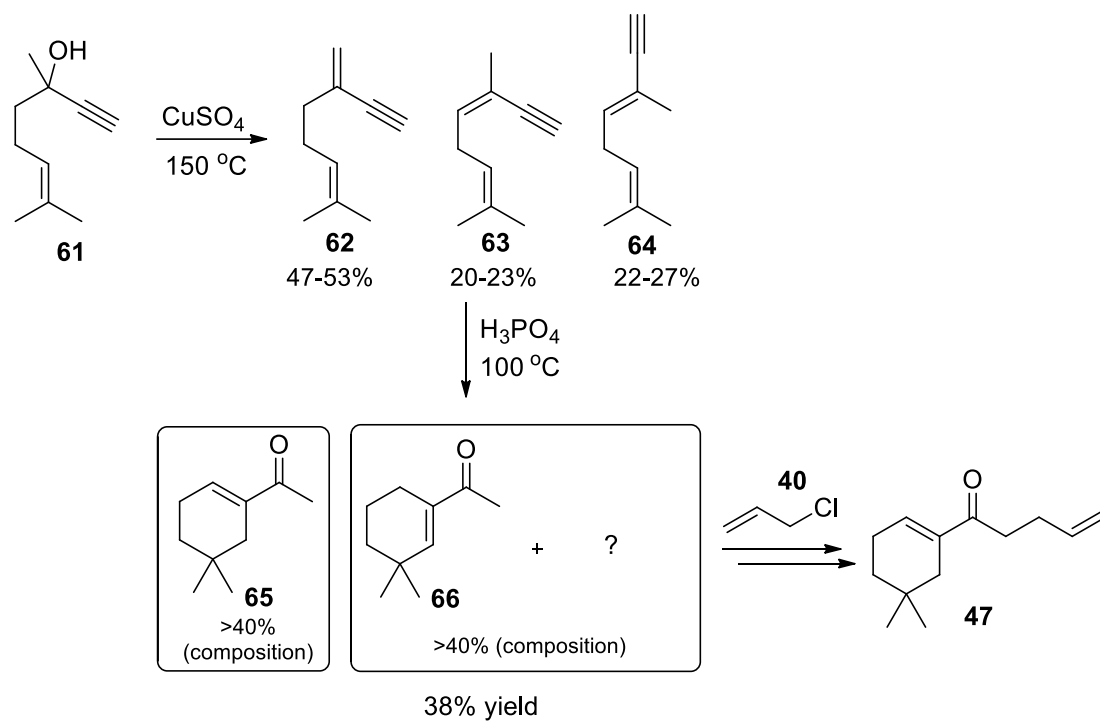
Another route started from dimedone **56** and in 7 steps gave a 1:1 mixture of product isomers (Scheme 8). Of the numerous routes reported in 1976, all yielded α/β mixtures of products which is still an issue that persists in today's industrial routes. The α - and β -isomers **47** and **55** are difficult to separate on large scale meaning that the product is therefore sold as a mixture of α - and β -isomers. The worldwide annual volume consumption for galbascone is estimated at 10 – 100 metric tonnes,⁶¹ meaning the demand for an improved synthetic route with higher selectivities with regards to product isomer composition is high.



Scheme 8: An early galbascone synthesis reported by Firmenich.

The route currently used by IFF is similar to that given in Scheme 7 starting from dehydrolinalool **61**. Direct acidification/Rupe rearrangement of dehydrolinalool is known to give almost exclusively the undesired β -product along with some pyran formation.⁶² This, however, is not the case for the dehydrated analogues **62** - **64**. In IFF's route, dehydrolinalool is therefore dehydrated prior to acid catalysed cyclisation, which produces a mixture of three products (Scheme 9), with two of these being α - **65** and β -dehydroherbac **66**. The initial dehydration is carried out as a reactive distillation in the presence of copper sulfate in a paraffin oil/toluene mixture, the latter is co-distilled with the enyne products **62** - **64**. The resultant solution of enyne isomers in toluene is then fed into a reactor containing phosphoric acid over a period of 12 hours. This process is conducted on a multi-tonne scale (9,000 kg dehydrolinalool) at IFF Benicarló and gives the product isomer in around 19% overall yield.

Allylation of these products gives galbascone, however, this step works well and so was not considered within the scope of this project. The objectives, therefore, were to better understand the cyclisation process associated with the dehydrated enyne isomers **62** - **64** and investigate alternate routes towards α -dehydroherbac **65** with the aim of attaining both a higher yield and improved α -selectivity (38% yield, ~50% isomeric purity).



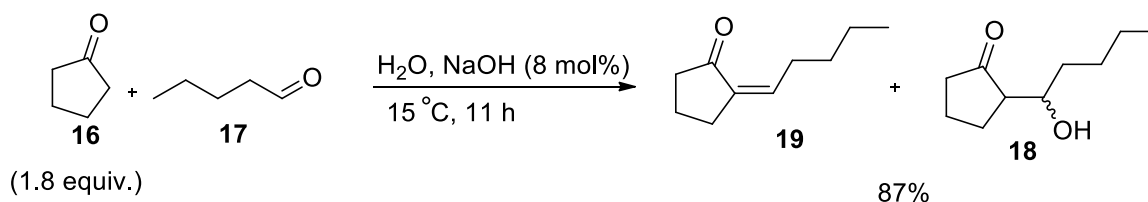
Scheme 9: IFF's current route towards the galbascone precursor, dehydroherbac **65**.

2. Results and Discussion

2.1. Hedione

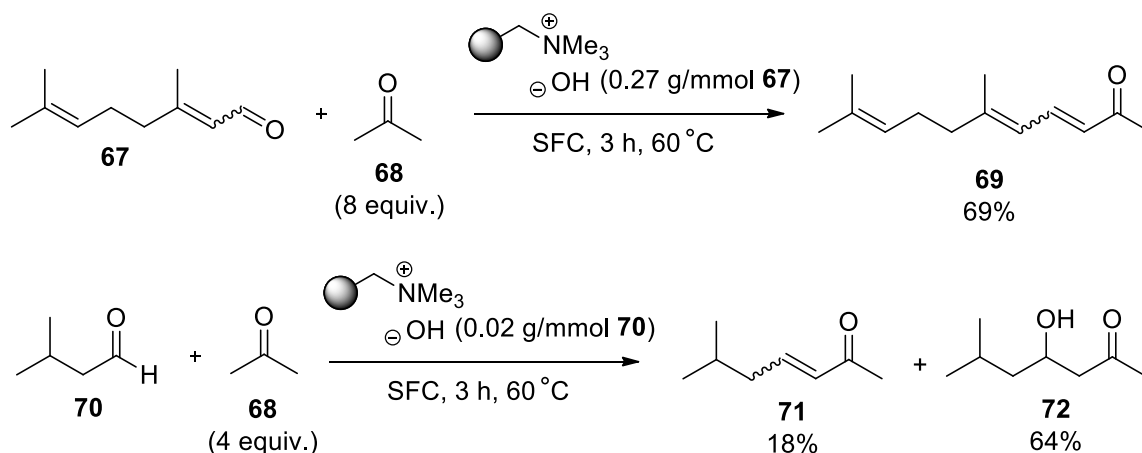
2.1.1. Preliminary Studies – Ambersep 900 OH-Catalysed Aldol Reactions

The industrial synthesis of Hedione is well established, highly cost effective and is currently conducted using batch processes (Scheme 1).³⁷⁻³⁸ Instead of trying to develop a completely new synthetic route towards Hedione, we therefore elected to assess the potential for conducting the industrial synthesis in flow. The first step in the synthesis of Hedione is an aldol condensation between cyclopentanone **16** and pentanal **17**. In batch, this is carried out as a two-step process using sodium hydroxide as a base to form a mixture of intermediate **18** and product **19** (Scheme 10). The mixture is subsequently enriched by treatment with acid to obtain pure **19**.⁶³



Scheme 10: Batch conditions for the aldol reaction of cyclopentanone and pentanal.⁶³

Recently, the strongly basic polymer-supported Ambersep[®] 900-OH has been used as a catalyst to effect aldol condensations for a range of compounds relevant to the F&F industry (Scheme 11).⁶⁴



Scheme 11: Ambersep 900-OH catalysed aldol reactions under solvent free conditions (SFC).

The Ambersep resin, initially developed for condensate polishing systems for fossil fuelled power generating stations, essentially comprises a macroporous cross-linked polystyrene matrix with the incorporation of trimethylammonium units where hydroxide acts as the counter-ion. Its use as a heterogeneous catalyst within a packed bed reactor in flow was attractive for the following reasons; a higher relative local stoichiometry and a higher productivity can be achieved per mass of catalyst, there is no need for filtration after the reaction and recycling of the catalyst is easy and efficient. Packed bed reactors are set up as shown in Figure 12, a flow stream is directed through the column while the solid-supported reagent remains static.

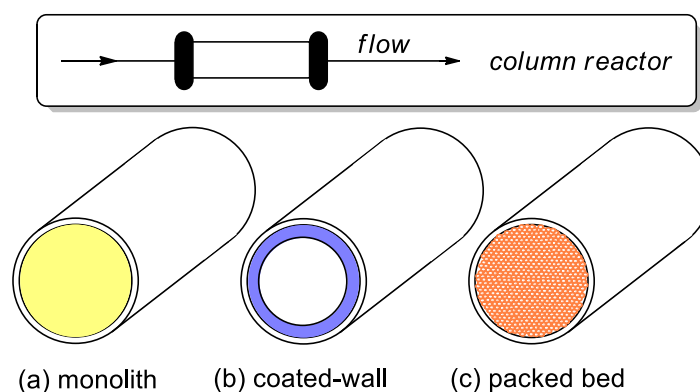
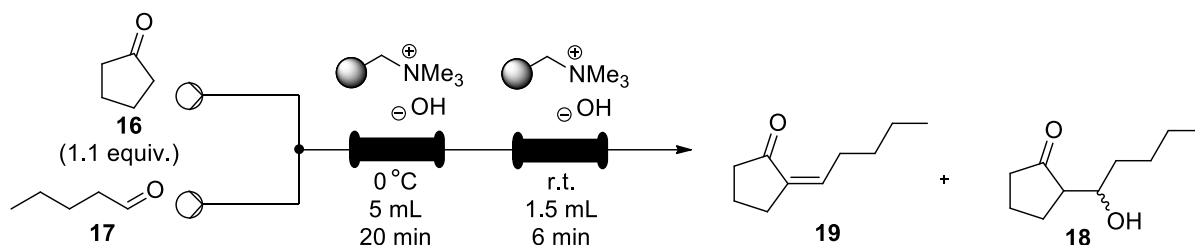


Figure 12: Immobilised reagent column reactor types.

After showing that the Ambersep catalysed reaction of cyclopentanone and pentanal worked well in batch (Figure 13 (b)), a short optimisation exercise led to a flow system in which two separate flow streams were used, one with neat cyclopentanone (1.1 equiv.) and the other with neat pentanal. These were directed into an Ambersep 900 OH packed column reactor (free volume 5 mL, residence time 20 min) maintained at ambient temperature and the product was collected at the reactor outlet. Under flow conditions, high levels of aldehyde self-condensation (**73**) and double addition (**74**) were observed (GC 3.3 min and 4.5-6.3 min respectively, Figure 13 (a)). This was mitigated somewhat using the setup shown in Scheme 12, which involved

active cooling of a primary reactor along with a second reactor in series at room temperature. This resulted in the crude GC trace shown in Figure 13 (yield of mixture not determined). A comparison of the outcome of the reaction with an analogous batch process (1.1 equiv. ketone, solvent free conditions) is given in Figure 13.



Scheme 12: Optimised Ambersep 900 OH catalysed aldol reaction.

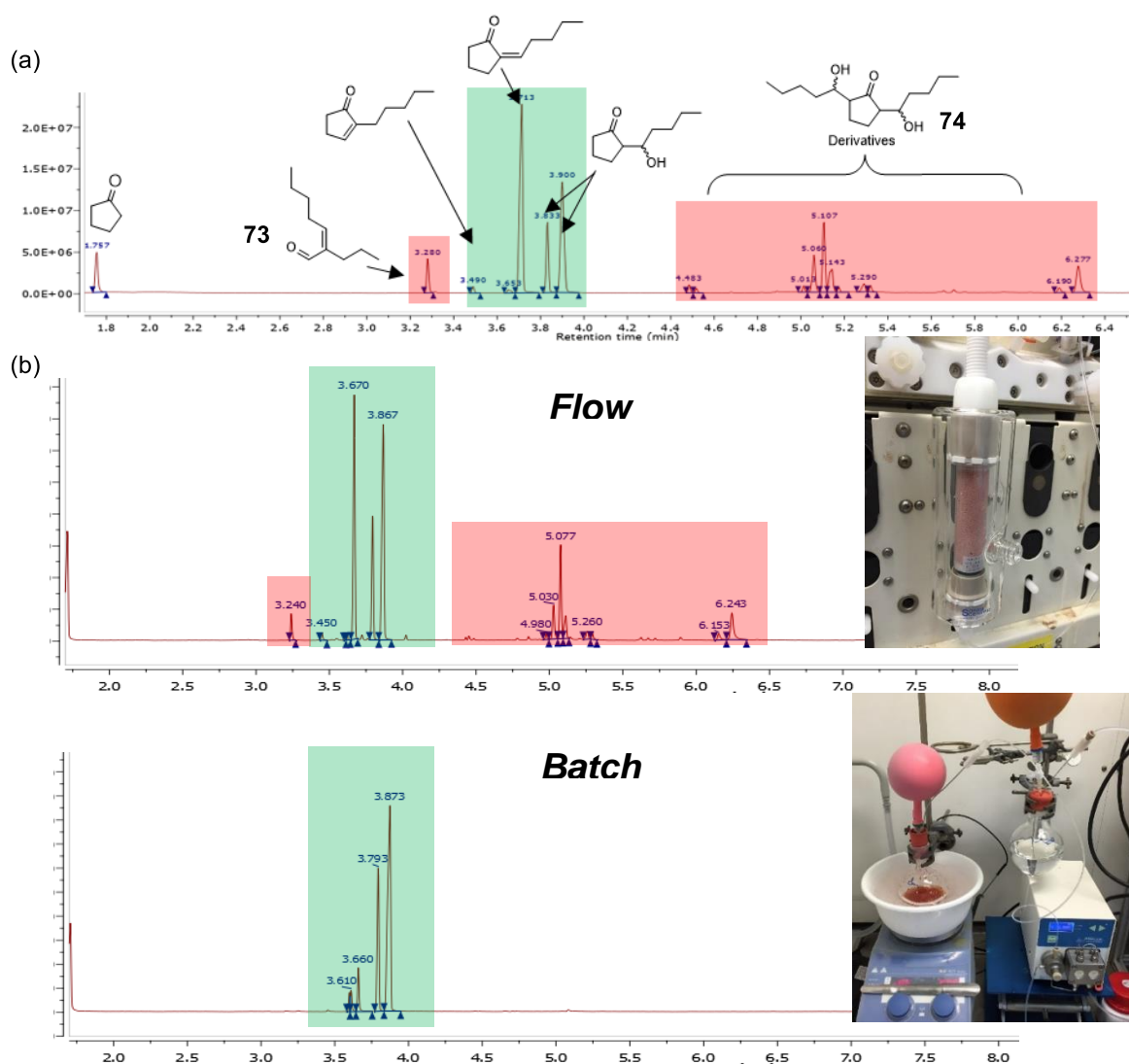


Figure 13: (a) Crude GC chromatogram of the reaction of cyclopentanone and pentanal catalysed by Ambersep 900 OH in flow. (b) GC chromatogram of optimised flow vs. batch procedures using Ambersep 900 OH.

One current issue when using flow chemistry is the difficulty of compensating for competing reaction kinetics by slowly introducing one reagent to an excess of another, as would be made possible in batch by ‘dropwise addition’. When carrying out the analogous batch operation, where the aldehyde was slowly added to a stirred mixture of the ketone and Ambersep 900 OH, superior results were obtained (Figure 13). No self-condensation of the aldehyde was observed in batch (3.3 min) and none of the double-addition products (4.5-6.3 min) were present either.

This issue was found to be even more problematic when more highly reactive aldehydes such as acetaldehyde and propionaldehyde were used. The comparative reaction of 4-isobutylbenzaldehyde **75** with acetaldehyde resulted in a complicated product profile when using Ambersep 900 OH. The formation of side products, resulting from self-condensation of acetaldehyde and over-reaction of the product **77**, could be attenuated to some extent by very gradual dropwise addition of acetaldehyde in batch, resulting in the GC trace shown in Figure 14. A flow protocol would therefore only realistically be feasible when using substrates that are not prone to self-condensation or over-reaction. As an illustrative example, the aldol reaction of furaldehyde **78** with octanal **79**, although sluggish, gave no side products in flow (Figure 15). While it still may be possible to translate the original methodology involving sodium hydroxide over to flow, there is no clear benefit to doing this. Controlling the addition rate of the aldehyde to an excess of ketone is the key to ensuring a high yield in aldol reactions between highly reactive aldehydes/ketones.

As a heterogeneous catalysed process, this represents a sequence that is not currently well suited to flow, since the slow addition of one reagent to another cannot be easily replicated in flow. This can also be said of aldol processes involving low molecular weight/highly reactive aldehydes and ketones in general. A flow synthesis of Hedione was therefore not explored further.

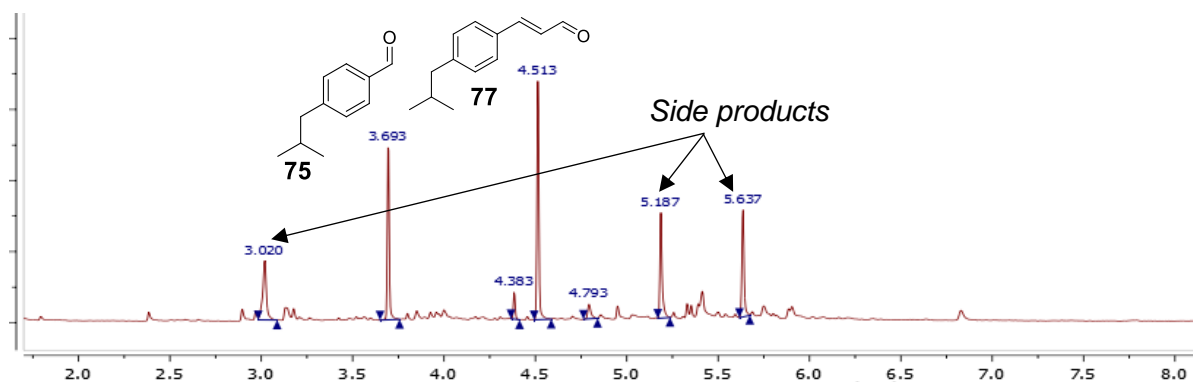
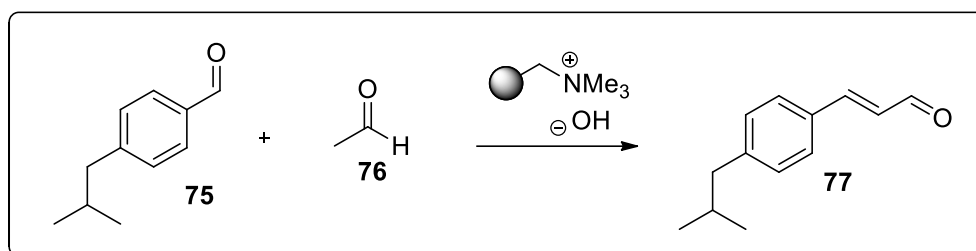


Figure 14: Crude GC of the Ambersep 900 OH catalysed reaction of 4-isobutylbenzaldehyde and acetaldehyde.

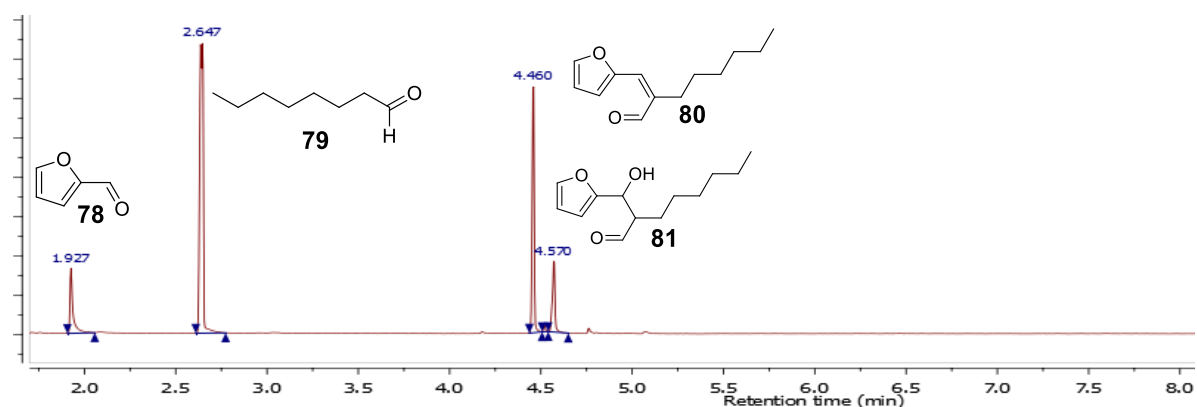
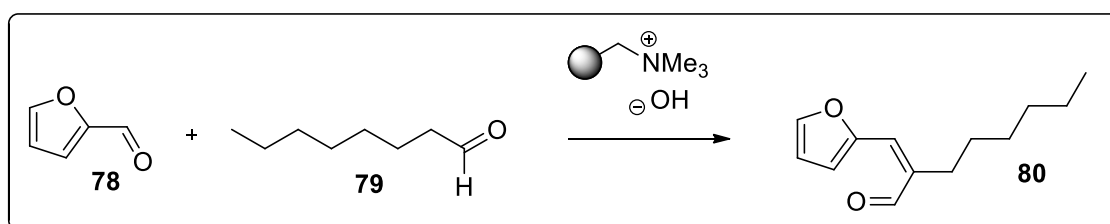
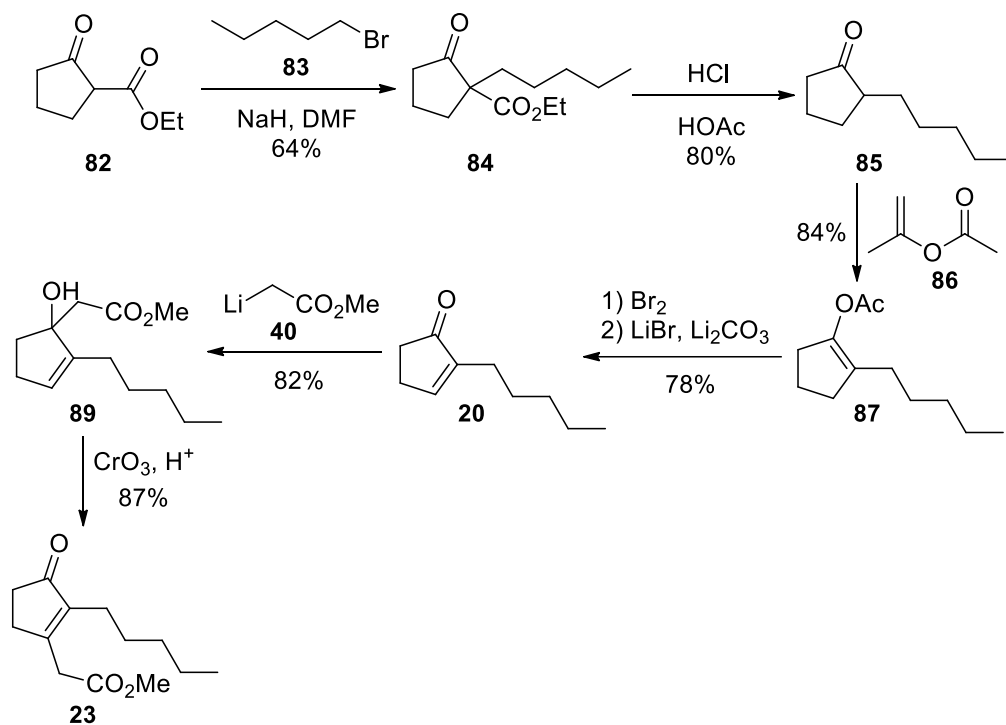


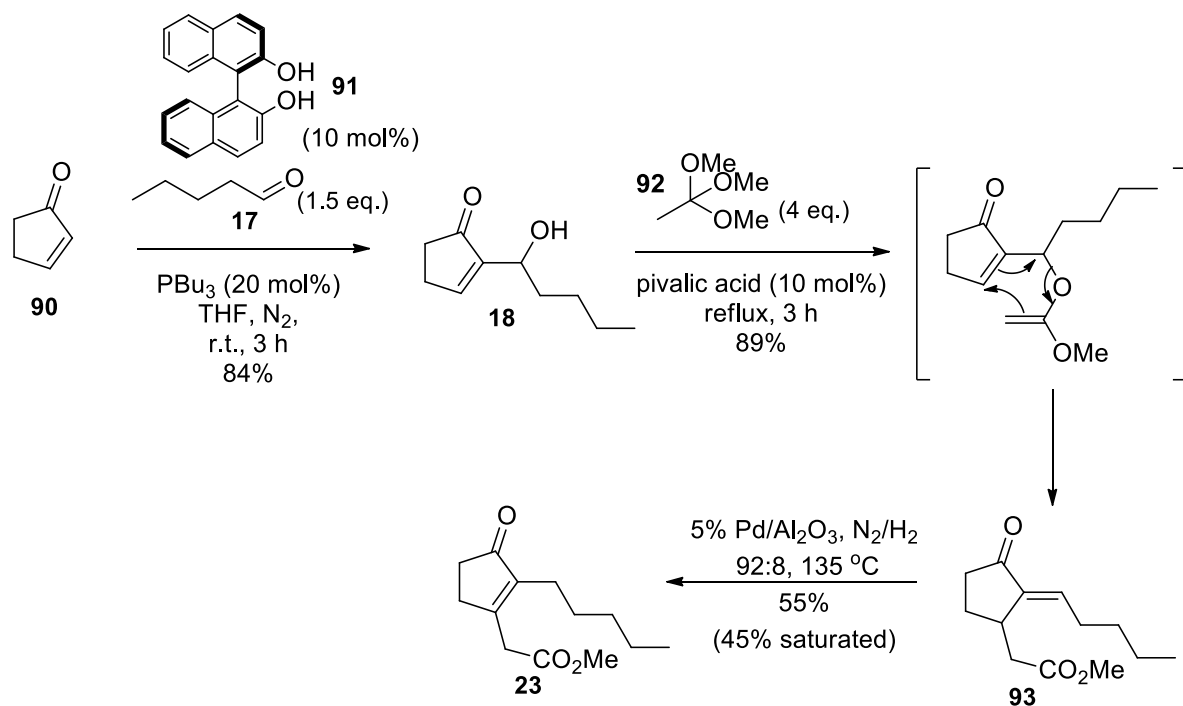
Figure 15: Crude GC of the Ambersep 900 OH catalysed reaction of furaldehyde and octanal.

2.1.2 Preliminary Studies - DHH Synthetic Routes

The development of DHH syntheses has been an active area of research for over 40 years. Early interest in to the compound resulted in the creation of quite lengthy syntheses such as that described by Ravid and Ikan in 1974 (Scheme 13).⁶⁵

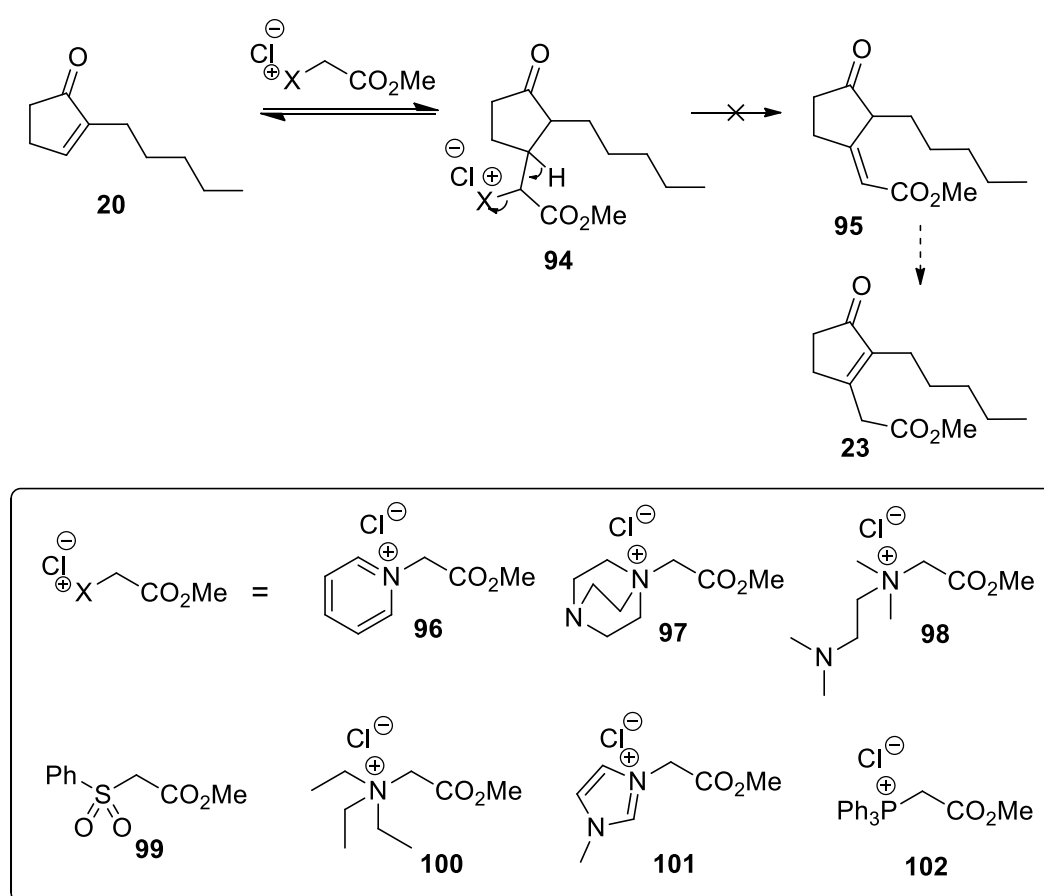


Scheme 13: A route to DHH as published in 1974 by Ravid and Ikan.

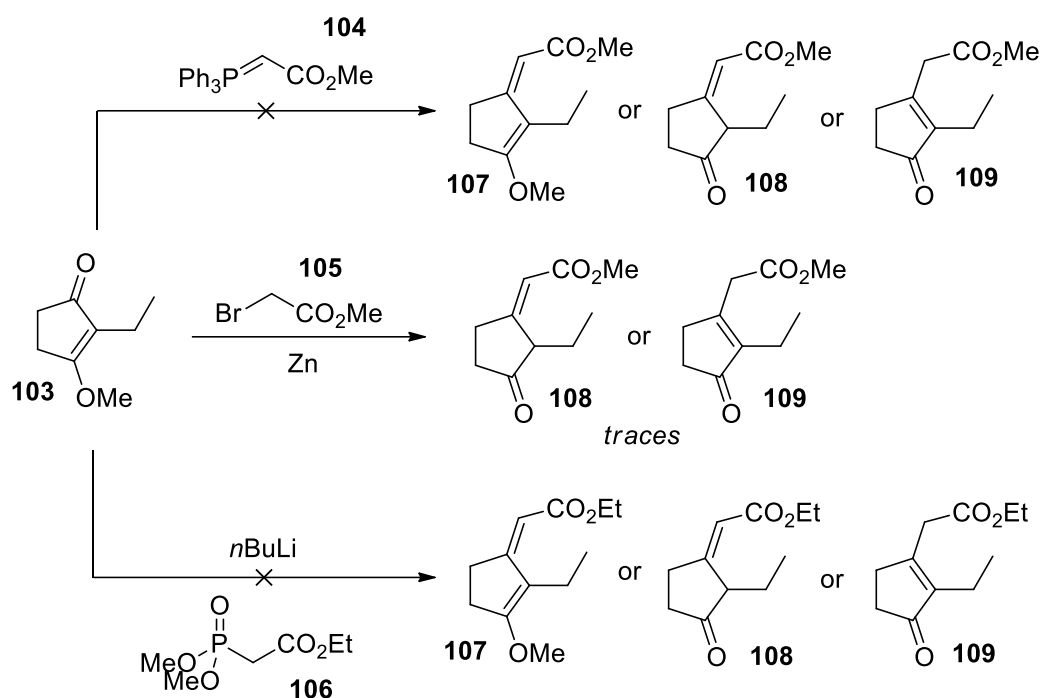


Scheme 14: Route to DHH developed by Chapuis *et al.*

Recent synthetic efforts have sought to reduce the number of steps required to make DHH by using modern synthetic techniques. Good examples of this can be found in the work of the Chapuis group at Firmenich, Geneva (one example is given in Scheme 14). An excellent overview of their additional findings as well as others' findings can be found in 2012 and 2013 reviews.⁴³⁻⁴⁴ The two primary routes shown in Scheme 15 and Scheme 16 outline our initial investigations. It was hoped that the route shown in Scheme 15 would deliver the product **95** which could then be isomerised to the more highly substituted double bond-isomer DHH. While adduct **94** was observed by HRMS, the product **95** failed to form. Using the enol ether **103** as a model substrate, it was also hoped that a Wittig-type reaction would deliver the analogous double bond isomer **108** which could again be isomerised to give **109** (Scheme 16). However, only traces of such products were observed at best through a Reformatsky process.



Scheme 15: Michael addition route explored during preliminary studies (chloride salts **96** - **102** prepared by Graham Miller, MChem project student 2014-15)⁶⁶



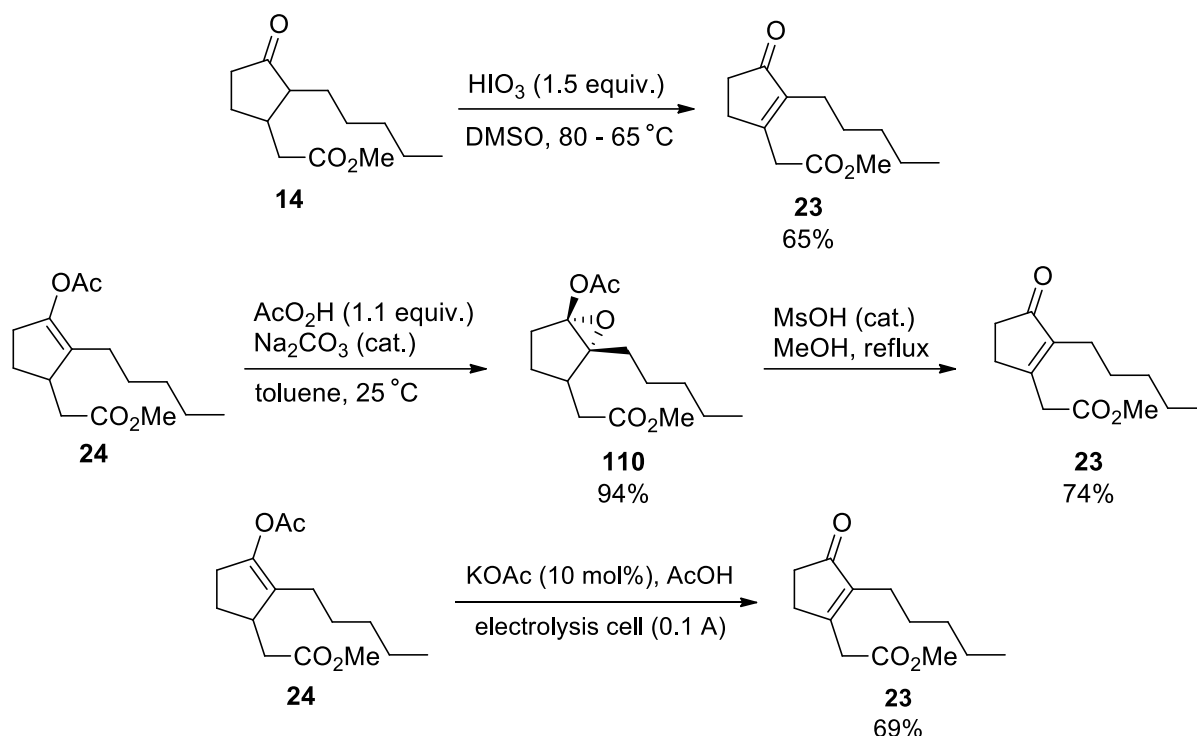
Scheme 16: Routes explored during preliminary studies.

These routes, as well as others described above, exhibit poor atom economy and make use of expensive reagents that would not justify them as replacements for currently used industry scale methodology. Hedione is sourced for approximately £5/kg. With this in mind, the oxidation of Hedione to DHH therefore became our main focus moving forward and these routes were not explored in any appreciable detail.

2.1.3. Hedione Oxidation Strategies

Numerous examples of DHH syntheses that start from both the enol-acetate **24** and Hedione **14** can be found in the literature. Examples include, direct HIO_3 oxidation of Hedione in DMSO,⁶⁷ peracetic acid epoxidation of the enol acetate (resulting in the α -acetoxy epoxide **110** which is then transformed into DHH by heating in MeOH with catalytic acid)⁶⁸ and anodic oxidation⁶⁹⁻⁷⁰ (Scheme 18). The competition between flavour and fragrance companies to effect this transformation at the lowest possible cost is high, making this an important area of

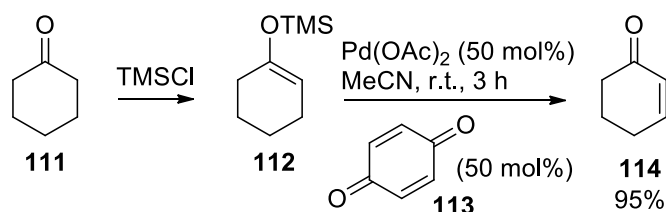
research. Our first strategy in terms of developing new methodology was to evaluate a metal-based approach.



Scheme 18: Known Hedione oxidation strategies.

2.1.4 A Copper(II) Bromide Mediated Oxidation

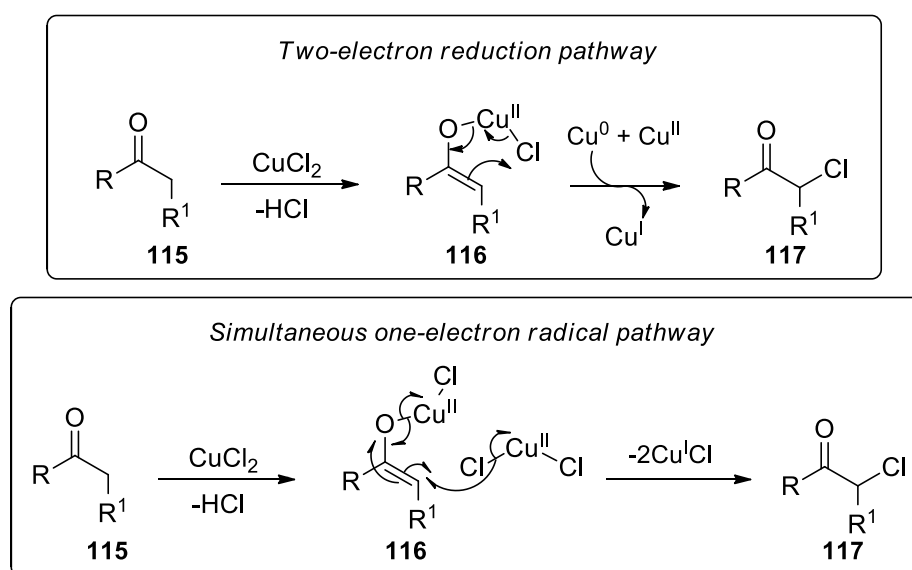
One classical way of preparing α,β -unsaturated ketones from their parent ketones is through the Saegusa oxidation (Scheme 19).⁷¹ The reaction was first discovered by Takeo Saegusa and Yoshihiko Ito in 1978 and many refinements to the original conditions have been made over the years (the Larock modification, for example, allows the use of 10 mol% Pd).⁷² However, large loadings of palladium salts are still generally required that really only justify its use on small scales or for preparing highly valuable products. A Saegusa oxidation therefore, would never offer a cost-effective means of DHH preparation at scale.



Scheme 19: The Saegusa oxidation of ketones.

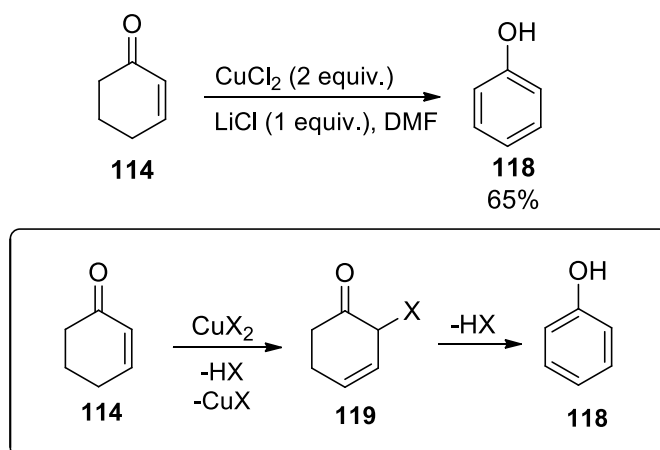
Copper(II) bromide and copper(II) chloride were first recognised as α -halogenating agents for ketones and aldehydes over 50 years ago. In 1963 Kosower *et al.* demonstrated their use for the halogenation of saturated⁷³ and unsaturated ketones.⁷⁴ These discoveries were stimulated by earlier work from Kochi (1955) where it was shown that carbonyl compounds were capable of reducing copper(II) chloride to copper(I) chloride through oxidation to their corresponding α -chloro ketones.⁷⁵

There are two proposed mechanisms for the chlorination (Scheme 20), both involving the initial generation of an enolate **116**. According to Kochi, coordination of the enolate to one CuCl_2 molecule occurs followed by a two-electron reduction of the copper with addition of the chlorine at the α -position **117**. The Cu^0 is then thought to be oxidised back to Cu^{I} by chloride exchange with a second molecule of CuCl_2 . Alternatively, a simultaneous one-electron reduction of two molecules of the copper(II) halide was proposed by Kosower. The mechanism again begins with formation of enolate **116** and coordination of one CuCl_2 molecule. A radical pathway was then proposed which results in the one-electron reduction of two separate Cu^{II} species, thus, generating two equivalents of CuCl directly. In both cases the same α -halo compound is formed.



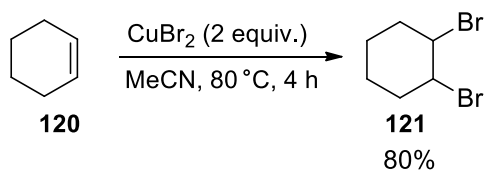
Scheme 20: Proposed CuX_2 halogenation mechanisms.

As well as chlorination of various ketones, Kosower also showed that it was possible to obtain phenols **118** from the treatment of cyclohex-1-en-2-ones **114** with 2 equivalents of CuCl_2 (Scheme 21).⁷³ Phenol formation can be modelled on these same mechanistic pathways. After an analogous first step, halide elimination of the α -halogented species **119** would be driven by the formation of aromaticity, giving the phenols **118**.



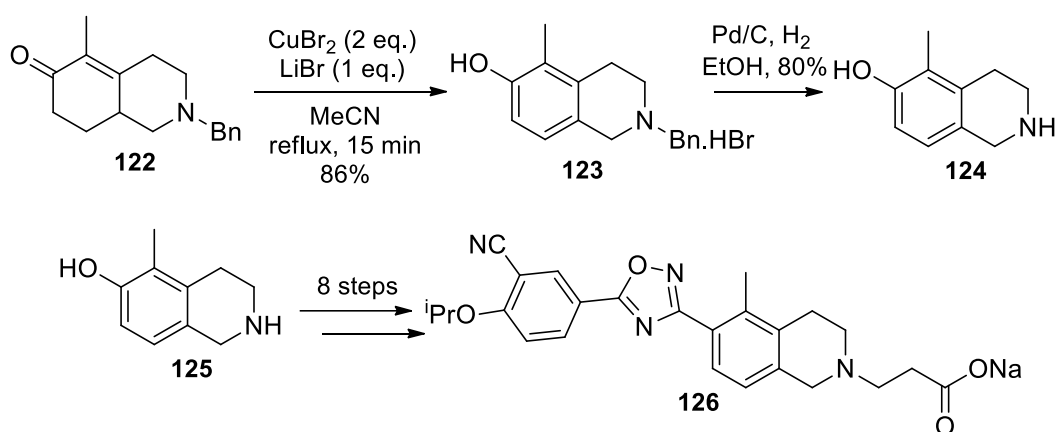
Scheme 21: The oxidation of cyclohex-1-en-2-one to phenol using CuCl_2 .

CuBr_2 induced bromination of alkene **120** to furnish the vicinal dihaloalkane **121** was also reported in 1971 (Scheme 22).⁷⁶ This was achieved for a range of substrates and CuBr_2 was found to be the most reactive of the halide salts. The use of MeCN as a solvent was also found to promote the reaction in the case of brominations but interestingly not chlorinations. This was ascribed to the higher dissociation energy of the less reactive CuCl_2 . The use of a methanolic solution and catalytic amounts of ligand have also proven effective in this respect.⁷⁷ More recently, CuBr_2 has been used to furnish a range of both mono and dibrominated species in the bromination of indoles⁷⁸ and electron-rich aromatics.⁷⁹



Scheme 22: Formation of vicinal dibromoalkanes using CuBr_2 .

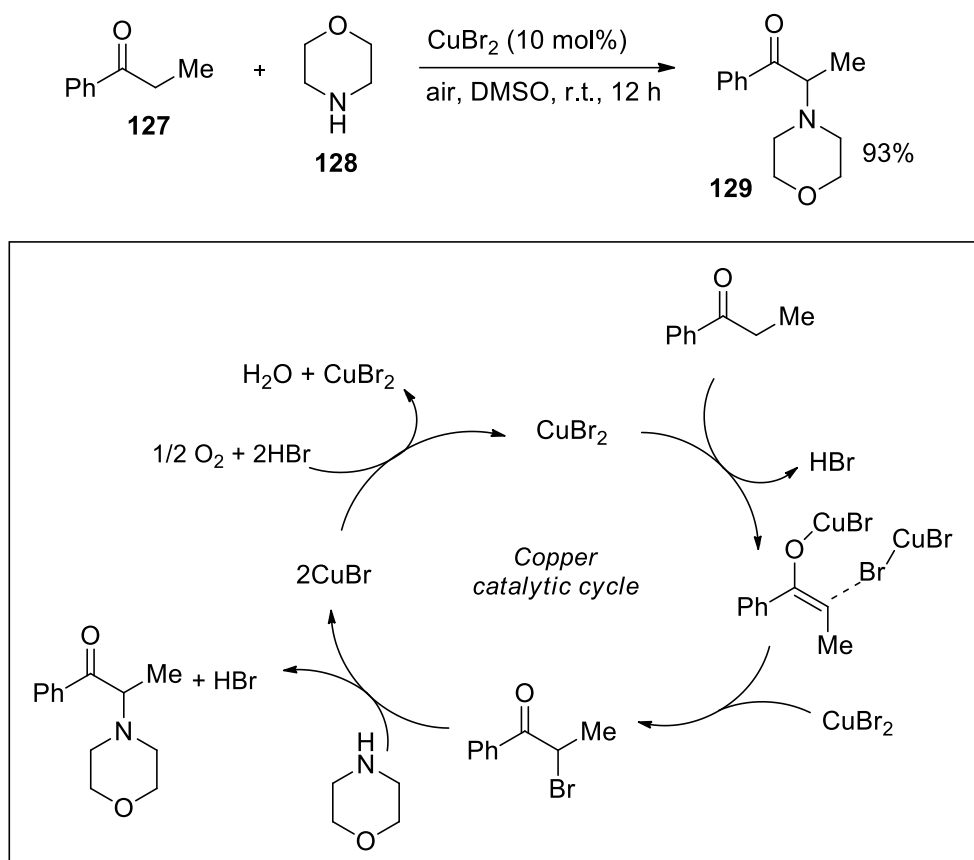
In 2013 CuBr₂ was used as an alternative to Pd(OAc)₂ to effect a Saegusa-type oxidation on a large scale for the synthesis of building block **122**, used in the preparation of an S1P₁ receptor agonist at GSK (Scheme 23).⁸⁰ The reaction bypasses the need for silyl enol ether formation—the first step of two in the previously used Saegusa route—and avoids the use of Pd(OAc)₂. This oxidation strategy was identified as the most promising of the many routes investigated and allowed the synthesis to be scaled up beyond the 7.7 kg scale that was previously reported.



Scheme 23: Use of CuBr₂ for large scale α -bromination by GSK.

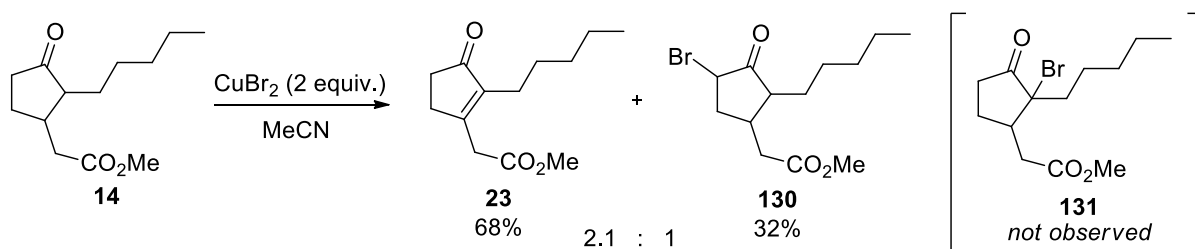
In 2013, a catalytic cycle based upon α -bromination-amination using CuBr₂ was reported by the Macmillan group.⁸¹ In their proposed cycle (Scheme 24), an α -bromo intermediate is formed which is intercepted by an amine such as **128**, displacing HBr. The reactions were carried out under an O₂ containing atmosphere allowing for regeneration of CuBr₂ according to the following redox equation: $2 \text{ CuBr} + 2 \text{ HBr} + 1/2 \text{ O}_2 \rightarrow 2 \text{ CuBr}_2 + \text{ H}_2\text{O}$. Similarly, a 2105 report discloses a CuBr₂ catalytic cycle based upon α -bromination-cyclisation.⁸² Employing such a catalytic copper redox system to effect an α -bromination followed by an elimination has never, to our knowledge, been reported. This kind of procedure has only previously been performed on α,β -unsaturated cyclohexanone starting materials with superstoichiometric

CuBr₂/Cl₂. This would, in theory, offer a comparable process to the Saegusa oxidation, where the use of palladium could be completely avoided.



Scheme 24: CuBr₂ catalytic α -bromination-amination.

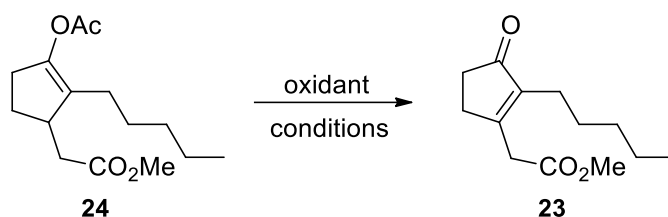
Preliminary experiments involved the treatment of Hedione **14** with 2 equivalents of copper(II) bromide, which led to bromination on both sides of the ketone (Scheme 25). Gratifyingly none of the α -bromo intermediate **131** was observed, suggesting that the proposed bromination-elimination was feasible and bromide elimination from **131** occurred spontaneously under the reaction conditions. The other α -bromo adduct **130** did not exhibit *in-situ* elimination.



Scheme 25: Products formed upon treatment of Hedione with two equivalents of CuBr₂.

In order to avoid the formation of the undesired α -bromo intermediate **130**, a directing group was employed. By reacting Hedione with isopropenyl acetate under acidic conditions, the enol acetate **24** was formed exclusively. Reaction of the enol acetate **24** with two equivalents of CuBr₂ in acetonitrile gave exclusively the desired product **23**. In an effort to better understand the reaction, the conditions given in Table 4 were screened.

Table 4: Screening of reaction conditions (1 mmol scale, 0.2 M solution, reflux unless stated otherwise).



Entry	Solvent	Oxidant (equiv.)	Time	Consumption ^a (%)	Yield ^a (%)
1	MeCN	CuBr ₂ (2.0)	5 min	100	92
2	toluene	CuBr ₂ (2.0)	30 min	40	0
3	MeOH	CuBr ₂ (2.0)	30 min	100	64
4	CH ₂ Cl ₂	CuBr ₂ (2.0)	30 min	66	0
5	CHCl ₃	CuBr ₂ (2.0)	30 min	45	0
6	THF	CuBr ₂ (2.0)	30 min	23	0
7 ^b	DMSO	CuBr ₂ (2.0)	30 min	84	0
8	MeCN	CuCl ₂ (2.0)	18 h	44	0
9	MeCN	Cu(OTf) ₂ (2.0)	18 h	0	0
10	MeCN	Cu(OAc) ₂ (2.0)	18 h	0	0
11	MeCN	CuBr ₂ (1.75)	5 min	100	77
12	MeCN	CuBr ₂ (1.5)	5 min	100	72
13	MeCN	CuBr ₂ (1.0)	5 min	100	53
14	MeCN	CuBr ₂ (0.5)	5 min	100	28
15 ^{c, d, g}	MeCN	CuBr ₂ (0.5)	24 h	0	0
16 ^{c, e, g}	MeCN	CuBr ₂ (0.5)	24 h	23	0
17 ^{c, f, g}	MeCN	CuBr ₂ (0.5)	24 h	0	0

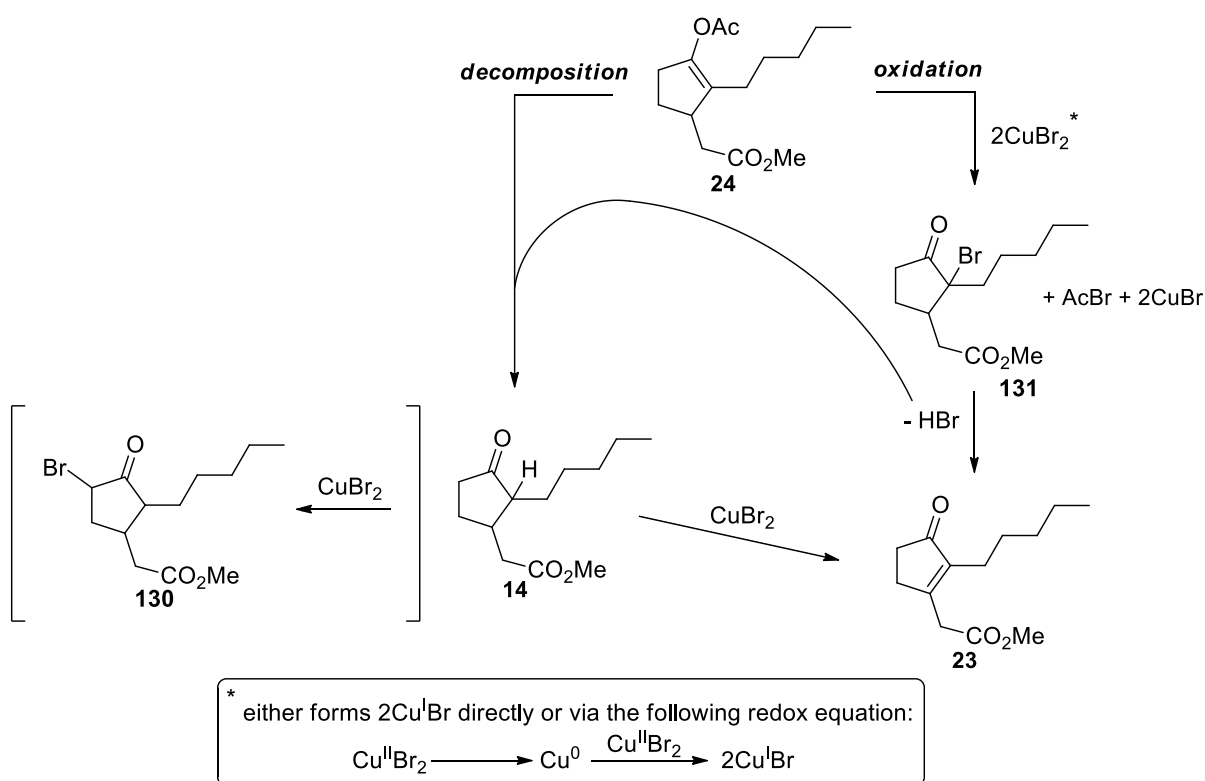
^a Yield/starting material consumption quantified using 2-nitrotoluene as an internal ¹H-NMR standard. ^b Conducted at 100 °C. ^c Carried out in an O₂ atmosphere. ^d DIPEA (5.0 equiv.) added. ^e Pyridine (2.0 equiv.) added. ^f 2,6-di-*tert*-butylpyridine (2.0 equiv) added. ^g Conducted at room temperature.

The formation of DHH **23** from the relevant enol acetate **24** was achieved in high yield (99% isolated, 92% NMR yield) using CuBr₂ (2 equiv.) in acetonitrile, at reflux after only 5 minutes. Of the other solvents screened, only methanol gave any appreciable amount of the product; this is consistent with previous literature observations in which CuBr₂ was used in MeCN.⁸² Of the additional copper(II) salts evaluated (chloride, acetate and triflate), none yielded any of the desired product, reinforcing the likelihood of a bromine-transfer mechanism. These findings imply solvent cooperation with regards to the proposed bromine transfer. Copper(II) complexes with both nitrile⁸³ and alcoholic ligands⁸⁴⁻⁸⁵ are well known and so the fact that, out of the solvents tested, the reaction was only compatible with MeCN and MeOH would suggest that a solvent-Cu(II) coordination is required to drive the reaction. The coordination of such ligands would serve to lower the Cu-Br dissociation energy and therefore facilitate the reaction.

Reducing the equivalents of CuBr₂ was found to be detrimental to the yield, suggesting that a catalytic system would be hard to achieve. For comparison, conditions under which a similar bromination was known to be catalytic in the literature⁸¹⁻⁸² were emulated (Table 4, entry 15 and 16) but these failed to generate any of the desired product. It was initially speculated that coordination of the bases used (DIPEA and pyridine) to copper led to deactivation of the bromination system. However, the use of 2,6-di-*tert*-butylpyridine as a non-coordinating base/proton sponge to negate decomposition was also unsuccessful (Table 4, entry 17). It was therefore concluded that the scavenging of protons by the bases was in fact causing deactivation and that the reaction is incompatible with a basic environment.

The system described in Scheme 26 is proposed as the principle mechanistic pathway, in which 2 equivalents of CuBr₂ are required. Initially a transient α -bromo intermediate **131** is formed which undergoes rapid elimination to give DHH **23**. The evolution of HBr occurs which is capable of promoting competitive deacetylation of the starting material **24** giving the saturated

compound **14** (Scheme 26). The rate of the oxidation pathway is far quicker than the corresponding decomposition which, in turn, is quicker than the reoxidation of Cu(I) to Cu(II) by the following known equation; $2\text{HBr} + \frac{1}{2}\text{O}_2 + 2\text{CuBr} \rightarrow 2\text{CuBr}_2 + \text{H}_2\text{O}$.⁸¹⁻⁸² The sequestering of HBr through formation of AcBr would also inhibit the potential copper reoxidation sequence. These indications imply that developing a catalytic process would be very difficult based upon the current acyl enol starting material **24**.



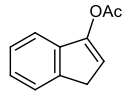
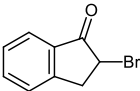
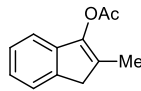
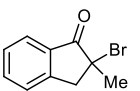
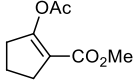
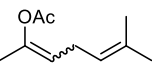
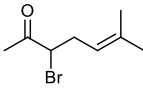
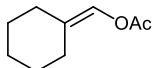

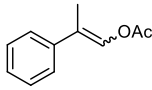
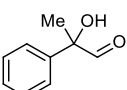
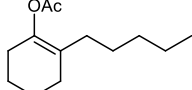
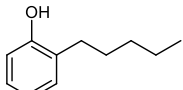
Scheme 26: Proposed oxidation/decomposition pathway for enol acetate **14**.

With a viable set of conditions in hand, the scope of the transformation was further investigated (Table 5). As indicated above, for unsymmetrical enolisable ketones, double bond regioselectivity could be problematic due to the initial enol acetate forming step leading to mixtures of products further down the line. Using Hedione, which exclusively gave a single enol acetate, none of the undesired enol bond isomer was observed. This approach was only problematic in certain cases (Table 5, entry 2a - 6a, ratios given) as easily identified by the characteristic olefinic signal in the ¹H-NMR (typically ~5.5 ppm). This is an obvious limitation

to the methodology as the mixtures, if not separated, give rise to α -bromo intermediates which lead to different products. A selection of substrates for which this would not be an issue were therefore also investigated (Table 5, entries 7-13).

Table 5: Substrate scope investigation.

Entry	Starting Material	Yield (%) ^a	Entry	Product	Yield (%) ^a
1a (24)		97 ^b	1b (23)		99 ^b
2a (132) (133)		64 (3:1)	2b (134)		90 ^c
3a (87) (135)		70 (8:1)	3b (20)		89 ^c
4a (136) (137)		78 (2:1)	4b (138)		20 ^c
5a (139) (140)		75 (1:1)	5b (141)		62 ^c
6a (142) (143)		53 (6:1)	6b (144)		17
7a (145)		76	7b (146)		31

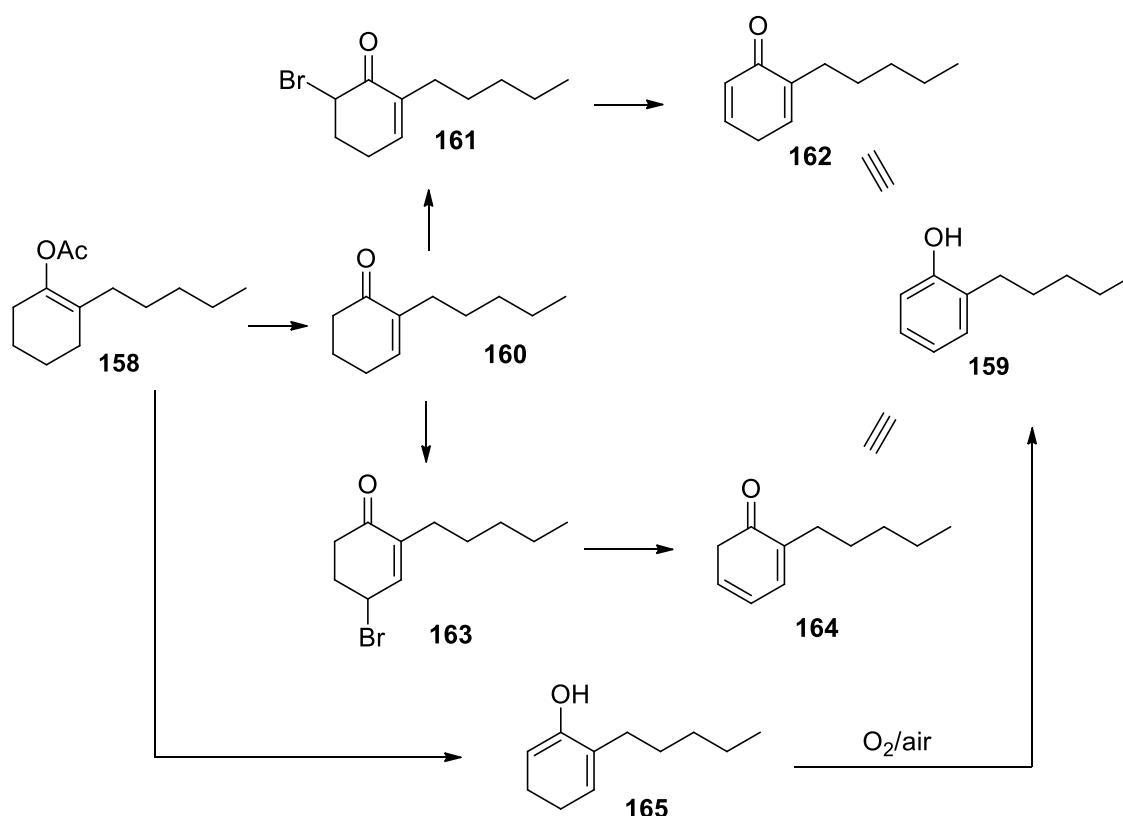
8a (147)		73	8b (148)		83
9a (149)		55	9b (150)		68
10a (151)		74	10b	-	N/A
11a (152)		67	11b (153)		46
12a (154)		64 ^d	12b (155)		86
13a (156)		89	13b (157)		57
14a (158)		57	14b (159)		42 ^e

^a Isolated yields after SiO₂ column chromatography. ^b Chromatography not necessary. ^c Yields reported relative to correct enol acetate isomer. ^d MsOH (10 mol%) and 4 equiv. isopropenyl acetate was used. ^e Unoptimised and based on 2 equivalents of CuBr₂.

In each case starting material consumption was quantitative (as determined by TLC). A general trend was observed regarding spontaneous elimination of the initially formed bromo intermediate. For the 2-substituted cyclopentanone derivatives (Table 5, entry 3-6), the pendant alkyl chain induced elimination at lengths down to the ethyl **141**, where incomplete elimination was observed. For both α -methyl cyclopentanone and α -methyl indanone (Table 5, entry 6 and 9) mixtures of α -bromo and α,β -unsaturated products were observed. In the case of **142** a complex mixture of products was obtained with **144** being the only isolable product after column chromatography. The unfunctionalised derivatives, **145** and **147**, yielded exclusively α -bromo adducts **146** and **148**. This trend suggests that steric impingement at the α -position is key in determining whether the substrate undergoes full elimination under the reaction conditions. Interestingly, the oxidation of **136** led exclusively to the formation of the

endocyclic, less conjugated double bond isomer **138**. Of the linear carbonyls tested (Table 5, entry 11-13), only α -bromination was observed. For the phenylpropenyl acetate, **156**, the α -bromo adduct formed initially, but underwent rapid hydrolysis during purification to give the α -hydroxy product **157**.

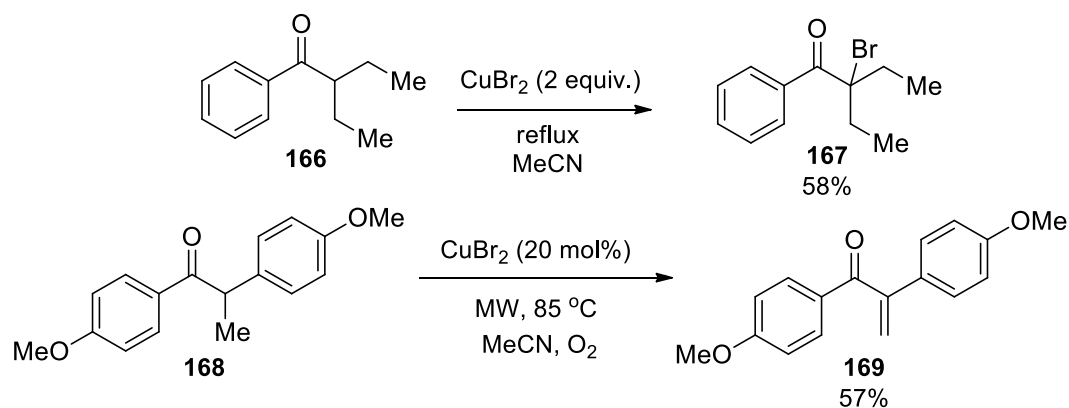
Interestingly, the cyclohexanone derivative **158** underwent successive oxidation furnishing the corresponding phenol **159**. The formation of phenols from α,β -unsaturated cyclohexanone starting materials using copper(II) salts is a known process and was first reported over 50 years ago.⁷⁵ However, taking an enol-cyclohexanone through a single-step, two-level oxidation process, to our knowledge, has never been performed. A speculative mechanistic rationalization is depicted in Scheme 27.



Scheme 27: Speculative phenol formation mechanistic routes.

As a proof of principle and using the information acquired from the above studies, we endeavoured to evaluate the possibility of a catalytic system. In this system, bromination should

be biased to only occur on one side of the ketone, leading to an elimination product which could not be brominated a second time. It was hoped that such a substrate could undergo complete conversion by using substoichiometric quantities of CuBr_2 .



Scheme 28: Substrates employed for establishing the validity of creating a catalytic system.

Attempted reaction of diethylacetophenone **166** (prepared *via* diethylation of acetophenone) was unsuccessful due to the formation of exclusively the α -bromo adduct, **167**. No elimination was observed; even upon treatment with 2 equivalents of CuBr_2 , only product **167** was isolated in 58% yield. Compound **168** was successfully prepared by α -methylation of desoxyanisoin. This was treated with 20 mol% of CuBr_2 and subjected to microwave heating (85 °C) under an oxygen atmosphere. The reaction progress was monitored by GC-MS analysis with O_2 purging of the reaction vessel between each sampling period (Figure 15). After 132 h, >85% conversion of the starting material **168** was estimated and the reaction was halted. After purification of the crude product by column chromatography and removal of a decomposition product **175** under high vacuum, **169** was obtained in 57% isolated yield. To ensure that the oxidation was not proceeding via an alternative route, for example, an α -hydroxylation, the reaction was repeated in an O_2 atmosphere with $\text{Cu}(\text{OAc})_2$ and without a copper catalyst. Neither of these conditions resulted in any conversion of the starting material. The α -bromo adduct **170**, was also observed in the crude reaction mixture by ASAP-MS (accurate mass obtained, $\Delta = 0.9$ ppm) supporting the proposed catalytic cycle (Scheme 29).

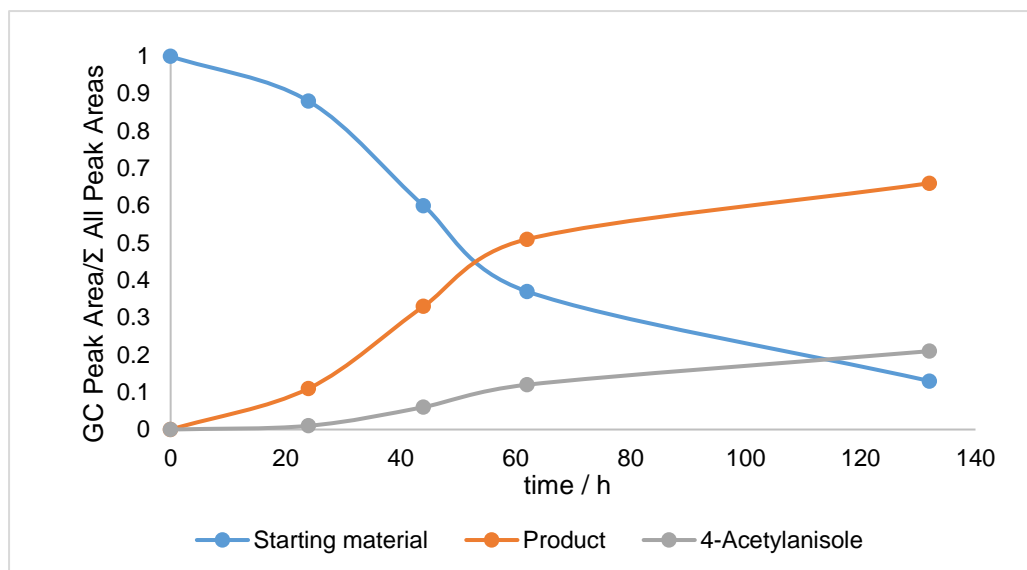
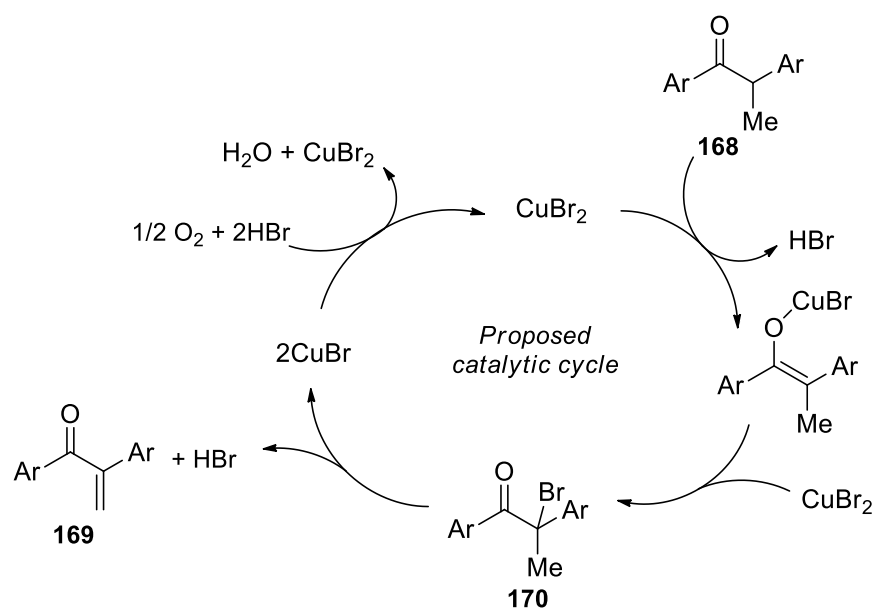


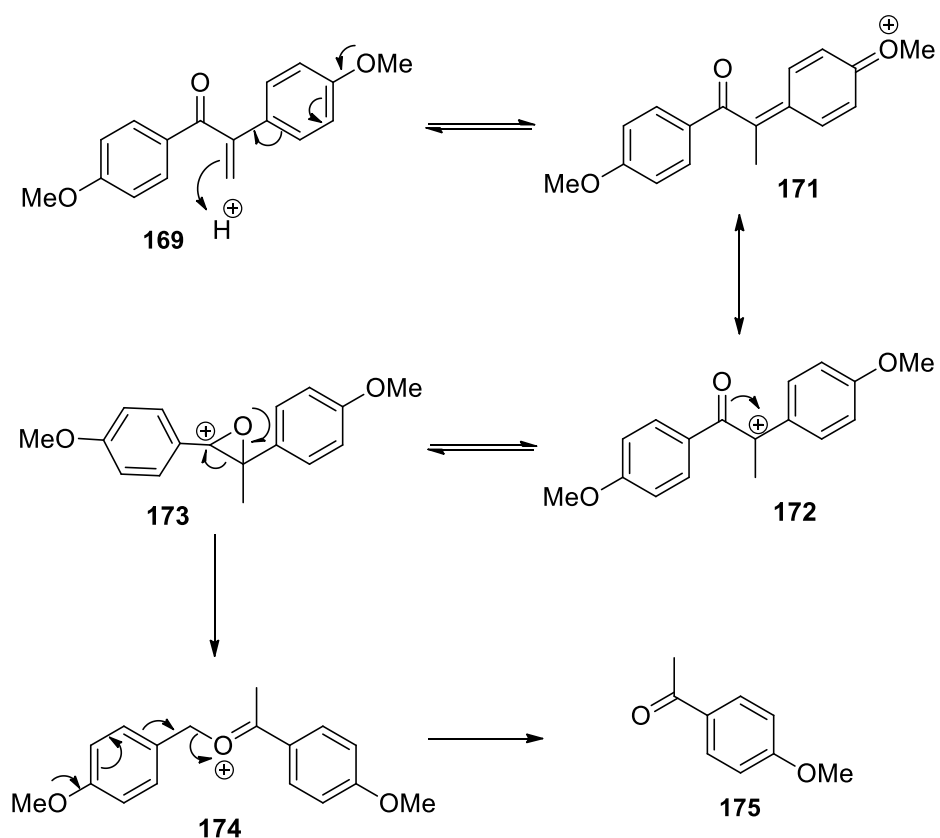
Figure 15: Reaction progression for the catalytic oxidation of **168**.

In our proposed catalytic cycle (Scheme 29), elimination leads to the formation of HBr which allows for the reoxidation of Cu(I) in the presence of oxygen, regenerating the brominating agent, CuBr₂. Decomposition of the product to 4-acetylanisole **175** was also observed under the acidic reaction conditions; this was presumably aided by the electron donating *para*-methoxy group on the aromatic rings. A possible mechanism for the formation of compound **175** is given in Scheme 30. The cycle described (Scheme 29) highlights the key attributes of the process and acts as a proof of concept, revealing that CuBr₂ could under certain limited conditions be used as a catalytic oxidant to convert saturated ketones to their corresponding α,β -unsaturated analogues.

Overall, this methodology has proved highly effective for the two-step synthesis of DHH from Hedione[®] and its applicability to other substrates was demonstrated. The fact that *in-situ* elimination is specific to substrates bearing sufficiently bulky functional groups at the α -position has also been evidenced. In addition, the catalytic example served as a mechanistic probe to gain better insight into the process.



Scheme 29: Proposed catalytic cycle for the oxidation of **168**.

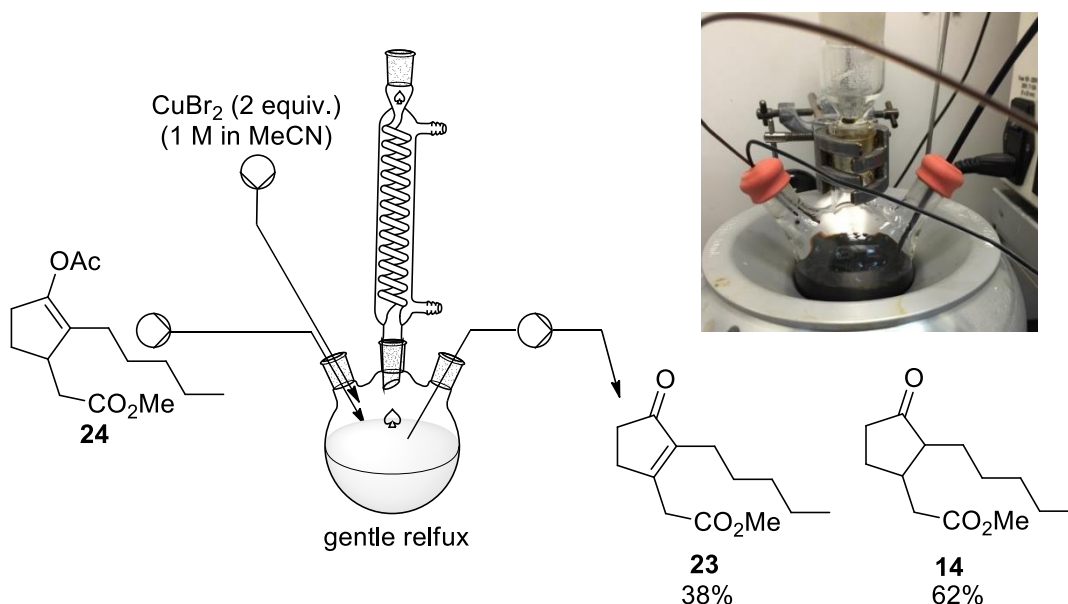


Scheme 30: Possible mechanistic pathway for the acid catalysed decomposition of **169**.

While an industrial synthesis of DHH based upon this methodology is not realisable due to the requirement for 2 equivalents of CuBr_2 which is prohibitive based upon cost, there is significant scope for adaptations to be used in other industry syntheses. There is potential for the application of both the catalytic system and the superstoichiometric system. The superstoichiometric system may also prove to be more financially viable in the pharma industry, for example, where intermediates and products tend to be of much higher value per mol than in the flavour and fragrance industry. We therefore sought to investigate the feasibility of a flow process.

2.1.5 Transposition of Copper(II) Bromide Methodology to Flow

We sought to investigate the potential for using the Hedione oxidation chemistry developed by ourselves in flow. The oxidation of the Hedione enol acetate **24** using superstoichiometric CuBr_2 was first studied in a continuous-stir tank reactor (CSTR) setup (Scheme 31).

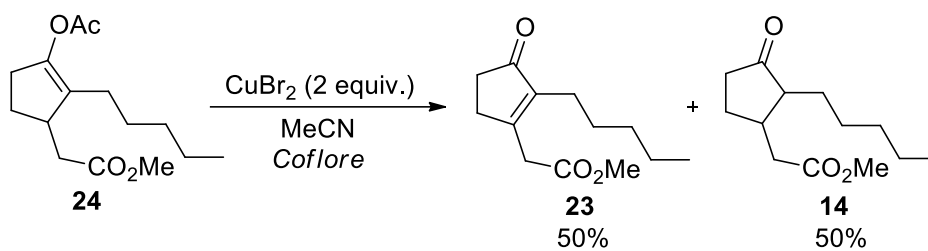


Scheme 31: CSTR reactor setup used initially.

Two inlets were used, one delivering neat enol acetate **24**, the other delivering a 1 M solution of CuBr_2 (2 equivalents), an outlet comprising a filter was used to avoid processing precipitates.

Using the same overall inlet/outlet flow rate ensured that the volume of liquid inside the reactor was constant, however, the precipitation of CuBr meant that the reactor had a finite lifetime. Once a working system had been established, the reaction could only be run for 20 min before clogging occurred. High levels of acid-catalysed starting material decomposition to Hedione were also observed due to the accumulation of HBr. The best result obtained with the CSTR setup was conversion of the starting material to 38% product and 62% Hedione. Presumably the CSTR was acting as a HBr reservoir meaning that the starting material was immediately exposed to a highly acidic environment upon entering the reactor which led to decomposition. It would be difficult to mitigate this with the above setup, we therefore considered an alternative approach.

The Coflore[®] agitated cell reactor (Figure 16) has been used to aid in the processing of solids in flow.^{19, 86} This is made possible by agitation (shaking) of the unit at frequencies between 1 – 10 Hz. It was proposed that by using such a setup as shown in Figure 16, wherein a stream of nitrogen was constantly passed through the reactor, the problem of acid-catalysed decomposition might be avoided. The whole reaction mixture would be processed continuously, meaning that HBr should not accumulate with the nitrogen serving to drive the HBr out of the unit as quickly as possible. The setup shown in Figure 16 was found to give the best results with heating at 70 °C. Using this setup the product was obtained in 50% yield along with Hedione. The levels of decomposition had therefore been reduced by 12% from the previous CSTR design, but avoiding decomposition altogether and obtaining comparable yields to the batch process was clearly challenging. The reactor (set up according to Figure 16) was run constantly for over 1 hour with no signs of clogging. While the issue of acid-catalysed decomposition makes this oxidation of **24** unsuitable for flow in this way, we have demonstrated the feasibility of a continuous process for the reaction with more stable substrates and that processing CuBr precipitates in flow would be possible using the Coflore ACR.



Scheme 32: Enol-acetate **24** oxidation in flow using the Coflore[®] ACR.

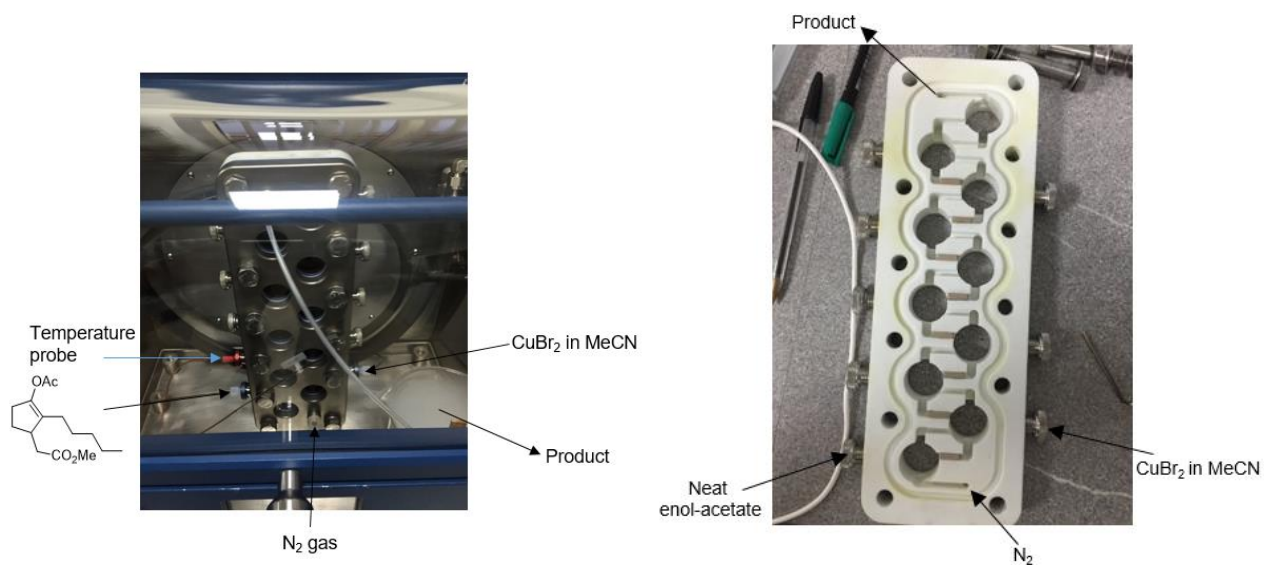


Figure 16: The Coflore[®] agitated cell reactor setup used.

2.1.6. A Strategy Based on Chlorination-Elimination

After discovering that the α -bromo adduct **131** undergoes spontaneous elimination under certain reaction conditions, we sought to develop a halogenation-elimination strategy that progressed through an α -chloro intermediate. Commonly used α -chlorinating agents for ketones include CuCl_2 ,⁸⁷ sulfuryl chloride (SO_2Cl_2 , **177**),⁸⁸ 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, **178**),⁸⁹ trichloroisocyanuric acid (TCCA, **176**),⁹⁰ *p*-toluenesulfonyl chloride,⁹¹ *N*-chlorosuccinimide (NCS, **179**),⁹² tetraethylammonium trichloride⁹³ and chlorine.⁹⁴ From earlier work,⁹⁵ CuCl_2 is known to be ineffective for Hedione oxidation. Of the remaining reagents, SO_2Cl_2 , DCDMH, TCCA and NCS were selected as they are cheap, readily available and ideal for use at scale, Cl_2 gas was also considered.

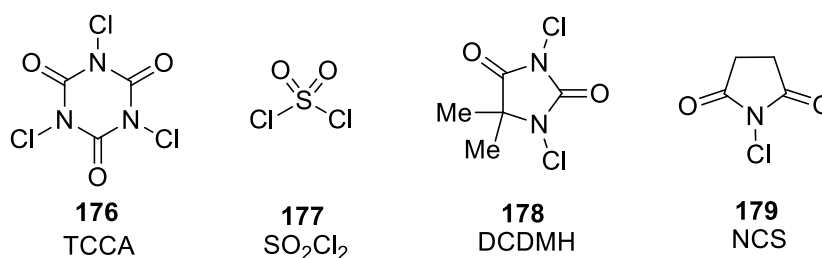
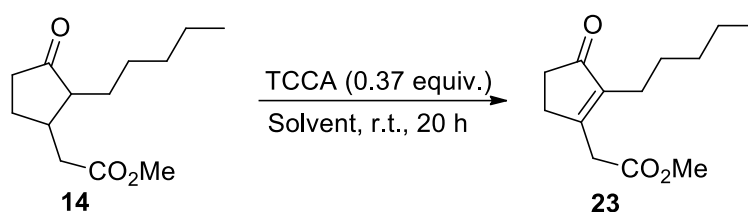


Figure 17: Structures of TCCA, DCDMH and NCS.

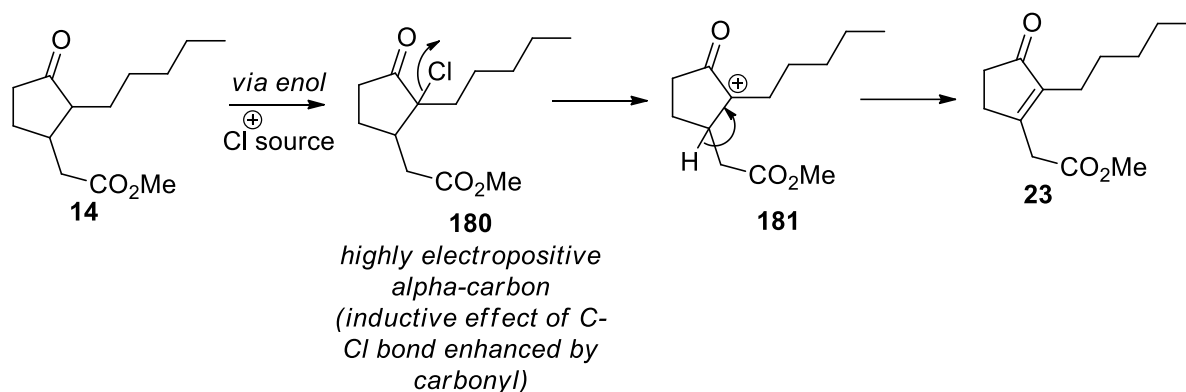
After initially considering starting from the enol-acetate **24** as with CuBr_2 , it was established that with TCCA **176** (a cheap industrial disinfectant and bleaching agent used in swimming pools and in the textile industry), the chlorination of Hedione **14** occurred with good selectivity towards the desired α -position. This indicated that including an extra acetylation step would not be necessary, subsequent initial studies looked to assess whether the proposed *in-situ* elimination of α -chloro intermediate **180** was feasible. A range of solvents were evaluated and it was found that the elimination occurred spontaneously when the reaction was conducted in methanol (Table 6). With other solvents partial chlorination was observed, but the subsequent elimination did not occur.

Table 6: Solvent screening for the TCCA oxidation of Hedione.

Entry	Solvent	¹ H-NMR yield ^a
1	CH ₂ Cl ₂	0%
2	toluene	0%
3	MeOH	21%
4	MeCN	0%
5	CHCl ₃	0%

Reactions conducted on a 5 mmol scale (1 M). ^a Calculated using 1,3,5-trimethoxybenzene as an internal ¹H-NMR standard.

E1 and S_N1 type mechanisms are known to be promoted by the presence of a polar solvent due to charge stabilisation of the required intermediary carbocation.⁹⁶ This presumably accounts for the observed relationship between solvent and propensity for direct elimination. It is understandable that methanol, as a polar protic solvent that allows for hydrogen bonding interactions, leads to the most efficient rate of elimination of the solvents tested. The proposed mechanism is given in Scheme 33. An E₂-type pathway would be disfavoured for two reasons; firstly, there is considerable bulk surrounding the reactive site of the molecule, restricting space for a concerted one step process requiring a single transition state. Secondly, the elimination is occurring across a C-C bond of a cyclopentane ring system. Rotation of the C-C bond is highly restricted which would make the antiperiplanar orbital alignment favoured in E₂ processes difficult to achieve. The mechanism is therefore likely to be more E₁-like in character (Scheme 33). Although the required carbocation in **181** would be adjacent to an electron-deficient carbonyl carbon, this would be stabilised through hyperconjugation from both the ring and pentyl chain.



Scheme 33: Proposed chlorination-elimination sequence.

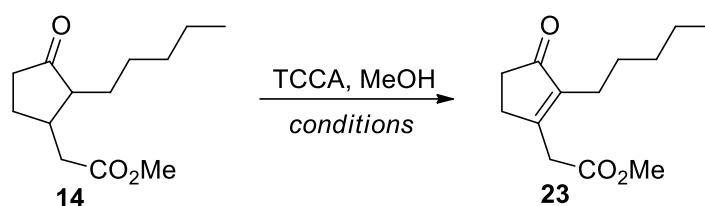
The chlorination reaction conditions were investigated using TCCA (Table 7). Gradual addition of the TCCA was required in order to control the temperature and avoid a runaway reaction. Adding the TCCA as a solution in methanol was initially thought to be the easiest way to achieve this, however, TCCA was found to be unstable in methanol unless stored in the absence of light. Hence, the solid was added directly to the reaction in portions such that the temperature was kept within the quoted range. At higher temperatures (Table 7, entry 1), the reaction occurred immediately upon addition of the TCCA which made controlling the temperature less challenging. At lower temperatures, however, a long and unpredictable delay was always observed between addition of TCCA and reaction initiation. This suggests that TCCA itself was not reacting directly with the starting material (as an electrophilic chlorinating agent) but that it was simply acting as a source of Cl_2 or Cl radicals and that these were the reactive species.

The observed delay can be explained by considering the fact that cleavage of an N-Cl bond in TCCA is first required in order to generate a chlorine radical/ Cl_2 and initiate the reaction. With radical initiators such as AIBN, this is classically achieved by heating or irradiating with uv-vis light.⁹⁷ By heating the reaction therefore, this ‘initiation’ can be induced and made to occur predictably. The initiation is highly exothermic and leads to a rapid propagation in the presence of additional TCCA. The key was therefore to initiate the reaction in the presence of a small

amount of TCCA and then dose the remainder of the TCCA afterwards, keeping the temperature within the desired window. Thermal initiation was found to occur within the range of 45 – 51 °C and it was also possible to initiate the reaction by irradiation with visible light (also previously demonstrated for the chlorination of chloro(methyl)pyridine with TCCA⁹⁸), further validating the proposed chlorination mechanism. The reaction proceeded smoothly and initiated at the same temperature in the presence of a radical scavenger (Na₂SeO₃, 10 mol%), suggesting that the α -chlorination occurs through reaction with Cl₂ and not through a radical transfer process.

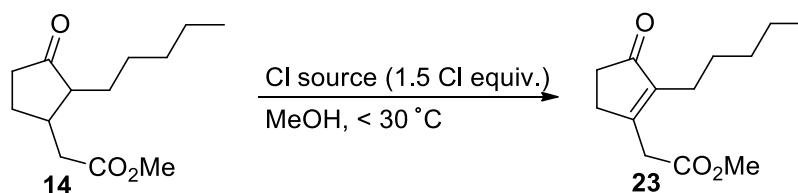
By performing the reaction at reflux a lower selectivity and yield was observed (Table 7, entry 1). The reaction was therefore heated briefly in the presence of ~5 mol% TCCA to induce initiation and then cooled intermittently while the remainder of the TCCA was added. In the presence of catalytic acid, the rate of the reaction was enhanced, however, poorer yields and selectivities were observed (Table 7, entry 2-3). The addition of acid also did not lead to initiation of the reaction. TCCA stoichiometry could be brought down to 0.33 equivalents without a drastic impact on yield (Table 7, entry 5 vs. 6) and using more than 0.5 equivalents resulted in a poorer yield (Table 7, entry 7) due to over-chlorination.

Using the conditions for TCCA (Table 7, entry 5), NCS, Cl₂ gas and DCDMH, were also employed (Table 8). Of these, the best yield was obtained with TCCA, with NCS giving the product in 48% and DCDMH resulting in a 35% yield as estimated by GC (*n*-undecane internal standard). Cl₂ gas was generated from TCCA in a separate vessel and bubbled into a solution of Hedione in methanol under a stream of nitrogen, this resulted in a 20% yield of the product. The fact that the product formed under these conditions reinforces the proposed chlorination mechanism - a reduced yield can be attributed to loss of Cl₂ through nitrogen purging.

Table 7: Chlorine source (reagent) screening for the oxidation of Hedione.

Entry	Conditions	GC yield ^a
1	Reflux, TCCA (0.5 equiv.), 20 h	36%
2	Thermal initiation → < 30 °C, TCCA (0.5 equiv.), HCl (2 drops), 20 h	48%
3	Thermal initiation → < 30 °C, TCCA (0.5 equiv.), HCl (5 drops), 20 h	35%
4	Thermal initiation → < 30 °C, TCCA (0.5 equiv.), SiO ₂ (0.5 g), 20 h ⁹⁹	47%
5	Thermal initiation → < 30 °C, TCCA (0.5 equiv.), 20 h	56%
6	Thermal initiation → < 30 °C, TCCA (0.33 equiv.), 20 h	51%
7	Thermal initiation → < 30 °C, TCCA (0.67 equiv.), 20 h	54% ^b

Reactions conducted on a 50 mmol scale (1 M in MeOH). ^a Calculated using *n*-undecane as an internal GC standard. ^b Product isolated by SiO₂ column chromatography in 52%.

Table 8: Chlorine source (reagent) screening for the oxidation of Hedione.

Entry	Reagent	GC yield ^a
1	TCCA	56%
2	NCS	48%
3	DCDMH	35%
4	Cl ₂ gas	20%
5	SO ₂ Cl ₂	75% ^b

Reactions conducted on a 50 mmol scale (1 M). ^a Calculated using *n*-undecane as an internal GC standard. ^b conducted as a two-step process, SO₂Cl₂ added in CHCl₃ followed by addition of MeOH after 5 h.

The use of sulfuryl chloride (SO₂Cl₂) was evaluated separately as the use of MeOH as the solvent would result in decomposition of the chlorinating agent generating the highly toxic dimethyl sulfate. Addition of methanol was still required in order for the α-chloro intermediate

181 to undergo elimination, therefore, the process was carried out as a two-step process. A solvent screen for the initial chlorination step was conducted (Table 9). The yield, as estimated by $^1\text{H-NMR}$, was found not to be greatly affected by the solvent used in the first step (72-74%) whereas conducting the reaction under solvent-free conditions led to a poorer NMR yield of 58%.

Table 9: Solvent screening for the oxidation of Hedione with SO_2Cl_2 .

Entry	Solvent	$^1\text{H-NMR}$ yield ^a
1	CHCl_3	73%
2	EtOAc	72%
3	toluene	74%
4	neat	58%

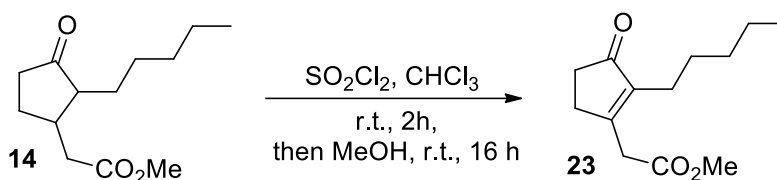
Reactions conducted on a 5 mmol scale (1 M). ^a Calculated using 1,3,5-trimethoxybenzene as an external $^1\text{H-NMR}$ standard.

Using SO_2Cl_2 , ‘initiation’ was not necessary with the reaction occurring immediately upon mixing with a solution of Hedione at room temperature and at 0 °C. This points towards a potentially different chlorination mechanism than is in operation with TCCA. It is likely that SO_2Cl_2 reacts directly with the enolised starting material, acting as an electrophilic chlorinating agent.

Gradual addition of SO_2Cl_2 was used in order to keep the temperature below 30 °C, however, the reaction was far less exothermic than with TCCA and hence much easier to control. Cooling during SO_2Cl_2 addition was found to be unnecessary and so was not used from this point onwards. The stoichiometry of SO_2Cl_2 was investigated (Table 10) and it was found that the number of equivalents could be reduced to 0.75 equiv. without a drastic effect on yield. The

reaction was then scaled up to 0.5 mol at an increased concentration of 2 M with no temperature or gas evolution control problems, indicating that the reaction is feasible for use at scale. Monitoring the reaction by both GC and NMR analysis revealed that the first chlorination step was complete in 2 hours and the second elimination step required 3 hours to reach completion (Figure 18). For this scale-up the product was isolated by vacuum distillation in 77% yield. It was observed that at this scale significant residues were left over at the conclusion of the distillation that still contained product.

Table 10: SO₂Cl₂ equivalents screening for the oxidation of Hedione with SO₂Cl₂.



Entry	SO ₂ Cl ₂ equiv.	GC yield ^a
1	0.5	48%
2	0.75	72%
3	1.0	75%
4	1.1	77% ^b

Reactions conducted on a 50 mmol scale (1 M). ^a Calculated using *n*-undecane as an internal GC standard. ^b Isolated yield - reaction conducted on 0.5 mol scale (2 M) and product isolated by distillation.

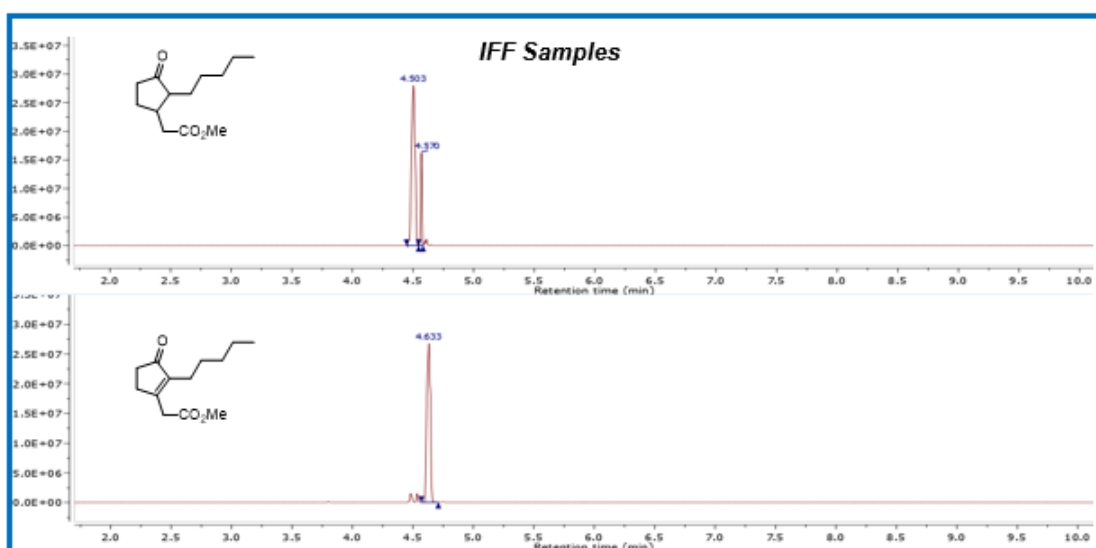


Figure 17: GC trace of IFF Hedione and DHH samples.

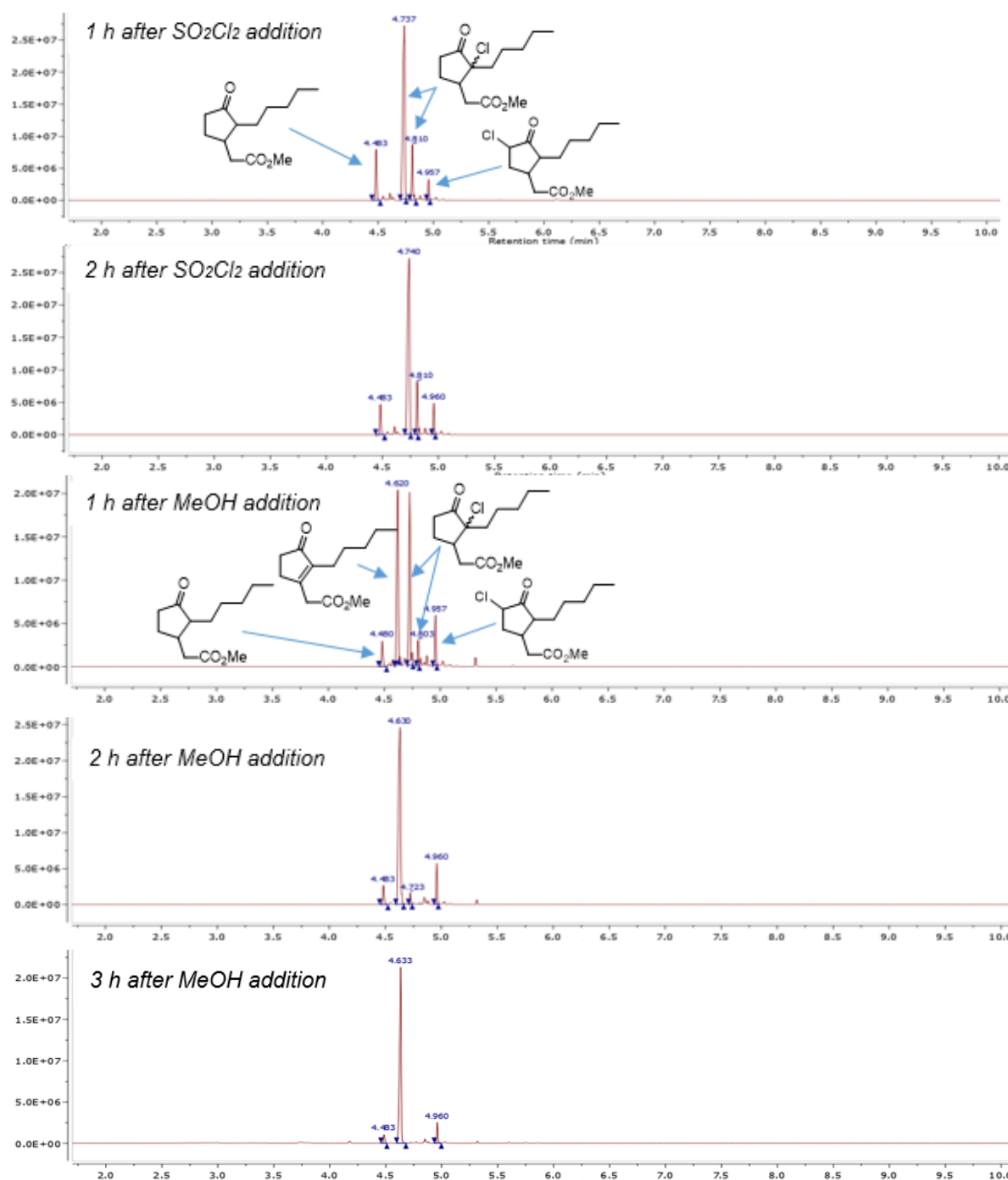
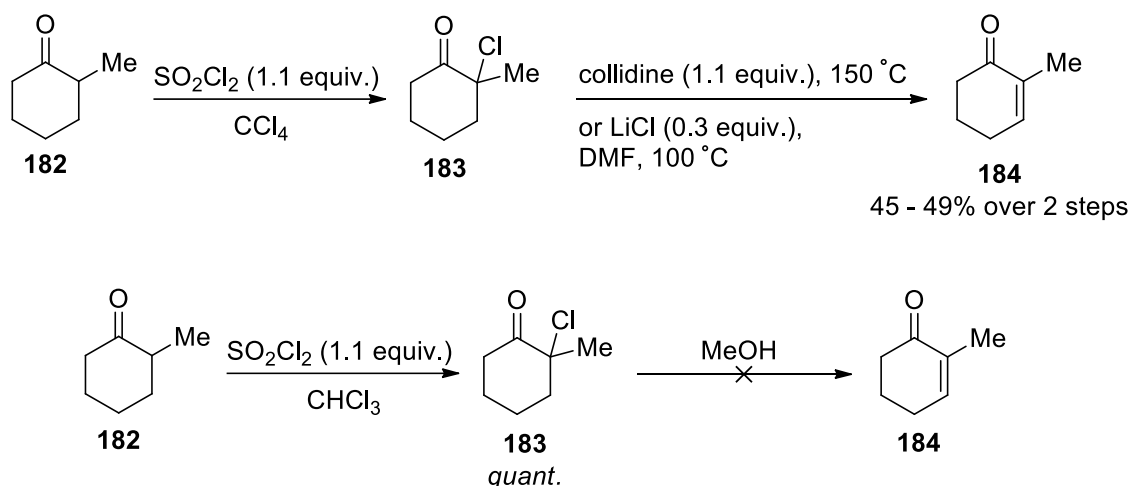


Figure 18: Monitoring of the reaction by GC-MS.

The optimum reagent for chlorination-elimination of Hedione was therefore shown to be SO₂Cl₂ (77% isolated yield vs. 56% with TCCA). While SO₂Cl₂ has been widely used as an α -chlorinating agent,^{88, 100} its use for a one pot chlorination-elimination process is completely new. In 1957, the use of SO₂Cl₂ for the synthesis of 2-methyl-2-cyclohexenone **184** from 2-

methylcyclohexanone **182** was demonstrated.¹⁰¹ However, this was performed as a discrete 2-step procedure wherein CCl₄ was used as a solvent for the initial chlorination and either collidine or a LiCl/DMF system was used to promote elimination in a completely separate reaction of a fully worked up α -chloro product **183**. For comparison, the conditions developed for the oxidation of Hedione were also applied to 2-methylcyclohexanone (Scheme 34). The α -chloro adduct **183** was formed quantitatively in less than 30 min, however, upon addition of MeOH no subsequent elimination was observed even after multiple days at elevated temperatures. This would indicate that, as with the CuBr₂ reaction, sufficient steric bulk at the α -position is required for *in-situ* elimination of the α -halo adduct.

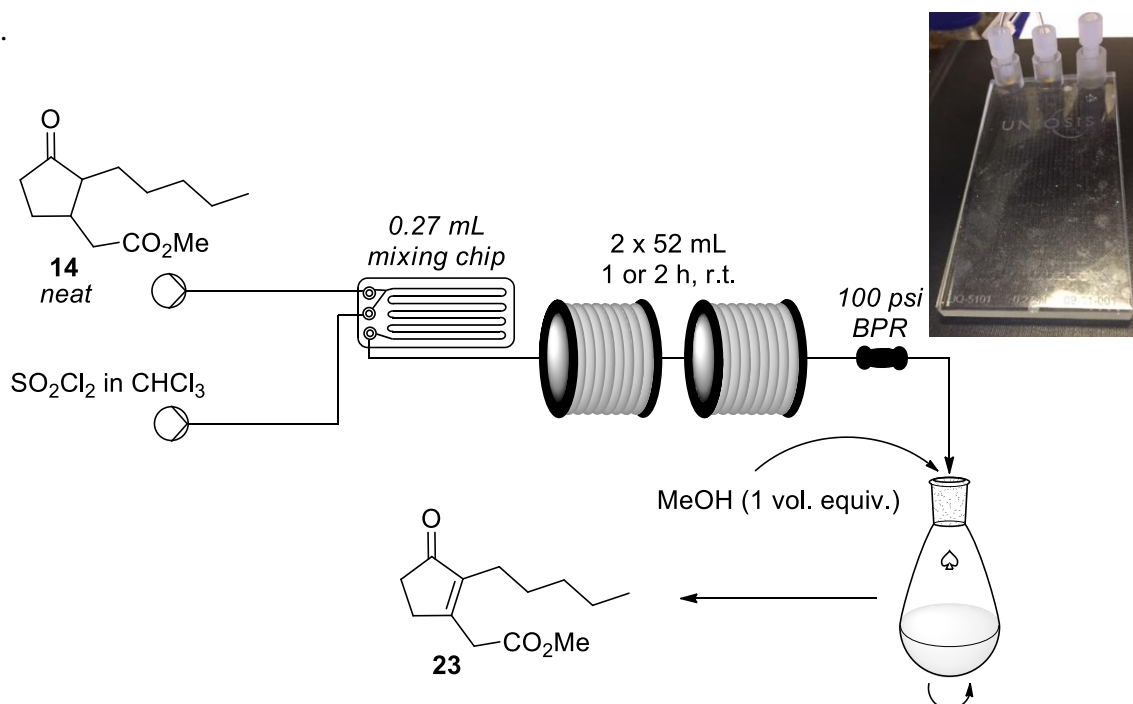


Scheme 34: 2-step sulfuryl chloride chlorination-elimination procedure reported in 1957 and application of developed reaction conditions to 2-methylcyclohexanone **182**.

Aside from the fact that SO₂Cl₂ gives the best yield of all chlorinating agents tested, its liquid nature (at room temperature) makes the process highly attractive in terms of transposition into flow. Another advantage in this regard is that no precipitates are formed during the reaction with SO₂Cl₂, as is the case with TCCA, NCS and DCDMH. The development of a flow process was next investigated.

2.1.7. Transposition of Sulfuryl Chloride Methodology to Flow

We sought to conduct the chlorination methodology developed for the oxidation of Hedione under flow conditions. The reaction with SO_2Cl_2 was ideally suited to flow due to the fact that all materials used were miscible liquids. Another feature of the reaction suited to flow was the fact that SO_2 gas evolution occurs. In batch, exothermic reactions that involve the evolution of gas are prone to overpressure and hence, very careful addition of reagents to the reaction mixture is necessary. In flow, gas evolution can be easily managed by regulating the pressure of the system with a suitable back pressure regulator (BPR). Using a pressurised flow system, gas evolution can be induced to only occur once the reaction stream has passed the BPR as it exits the reactor. Hence the gas is expelled from the reaction media in a constant and controlled manner.



Scheme 35: Flow setup used for the SO_2Cl_2 oxidation of Hedione.

A semi-continuous system was devised in which the chlorination step was performed in flow and the subsequent elimination was performed in batch (Scheme 35). Neat Hedione was fed into a 0.27 mL Uniqsis mixing chip along with a solution of SO_2Cl_2 in CHCl_3 at a rate such that 1.1 equiv. of SO_2Cl_2 was used with a residence time of either 1 or 2 hours within the

subsequent reactor(s). The flow system was pressurised using a 100 psi (6.9 bar) BPR for the chlorination step and the outlet was collected in a RBF. Upon halting collection, MeOH was added to the product mixture to induce elimination of the α -chloro intermediate **180**, at this point the reaction was left to stir overnight at r.t. (~16 h). The process worked well and gave comparable yields to the batch process (78% vs. 77%, Table 11, entry 2 vs. Table 10, entry 4) under the conditions initially tested (Table 11, entry 1-2). Improved heat dissipation meant that the exotherm was well controlled and the SO₂ gas evolution was steady and controlled upon the stream passing the BPR, a 100 psi BPR was sufficient to keep all gas in solution within the reactor.

Table 11: Screening for the oxidation of Hedione with SO₂Cl₂ in flow.

Entry	SO ₂ Cl ₂ conc.(M)	Reaction conc.(M)	time (h) ^a	GC yield ^b
1	1	0.76	1	74
2	1	0.76	2	78
3	3	1.69	1	67
4	6	2.45	1	60
5	1.45	1	1	72 ^c

Reactions conducted on a 5 mmol scale (1 M). ^a Residence time for first step. ^b Calculated using n-undecane as an internal GC standard. ^c Isolated yield of 35 min. sample collection – product isolated by SiO₂ column chromatography.

Higher reaction concentrations translate to higher throughput of product in flow, it was therefore desirable to attempt to increase the concentration in an effort to boost the throughput (throughput at 0.76 M = 12 g/h). This however, proved detrimental to the yield due to lower selectivities at higher concentrations (Table 11). A final scale-up was performed at 1 M and the reaction was run for 8 h, a 35 min sample was taken and treated with MeOH before the

product was isolated using column chromatography in 72% yield. Conducting the reaction as a semi-continuous flow process in this way is therefore feasible, allows for safe and controlled release of SO₂ and gives comparable yields to the batch process. There is no reason why the second step could not also be conducted in flow, creating a fully continuous flow process.

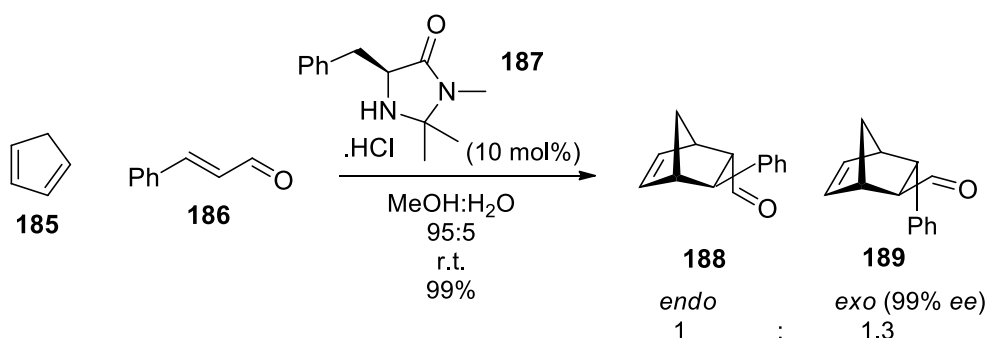
2.1.8. Summary and Conclusion

Following preliminary studies, the focus of this exercise became the oxidation of Hedione to DHH, for which two new methods were developed. The first required the use of superstoichiometric CuBr₂ and has been deemed unsuitable for use at scale, however, its applicability to other substrates was demonstrated and a catalytic system was also demonstrated. The second method made use of a one-pot chlorination-elimination sequence which was demonstrated for a range of chlorinating agents, the best of these was sulfuryl chloride. A flow process which was suitable for use at scale, allowing for safe and constant release of sulfur dioxide for the reaction mixture, was also developed. The batch sulfuryl chloride process has been deemed economically feasible for use at scale and is currently being trialled within a pilot plant.

2.2. δ -Damascone - A Lewis-Acid Catalysed Diels-Alder Reaction

2.2.1. Organocatalytic Approaches

The first alternative method for the catalysis of the Diels-Alder (DA) reaction between mesityl oxide and *trans*-piperylene (Scheme 6) investigated organocatalysis. Promotion of DA reactions using organocatalytic techniques has become an increasingly important tool for organic chemists in recent years. Work by MacMillan at the turn of the century showed that it was possible to promote Diels-Alder reactions between dienophiles comprising an α,β -unsaturated aldehyde system in an enantioselective manner using ‘iminium ion catalysis’ (Scheme 36).¹⁰² The formation of an iminium intermediate by condensation of a secondary amine with the carbonyl-containing dieneophile leads to a ‘LUMO lowered’ π -system, which is more favourable for cyclisation.



Scheme 36: Imidazolium catalysed Diels-Alder reaction.¹⁰²

Exploiting this methodology would potentially allow for much lower catalyst loading levels than are currently used and a much cleaner and less wasteful work-up procedure. Recent work showing that it is possible to transpose these reactions to flow also made this approach attractive.¹⁰³ A small series of secondary amines (Figure 19) was thus prepared and employed for the proposed reaction (Scheme 37). The relatively hindered imidazolidinone **187** was prepared according to the literature¹⁰⁴ but when applied to the reaction, led to no conversion when employed in up to 50 mol% under literature conditions. It was thought that the bulk surrounding the secondary nitrogen of this species was preventing iminium ion formation with

mesityl oxide so some less hindered amines were also investigated (**190** - **192**). However, a general lack of reactivity was observed in all cases, suggesting that this kind of catalysis is simply not compatible with mesityl oxide as a dienophile. This would explain the distinct absence of mesityl oxide's use as a substrate for these kind of processes in the literature. Furthermore, there are an abundance of examples where substrates such as methyl vinyl ketone and phenyl butanone are used.¹⁰⁵

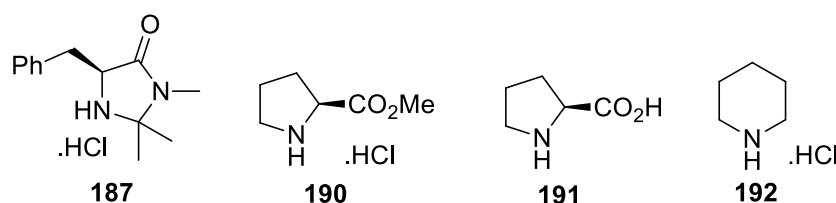
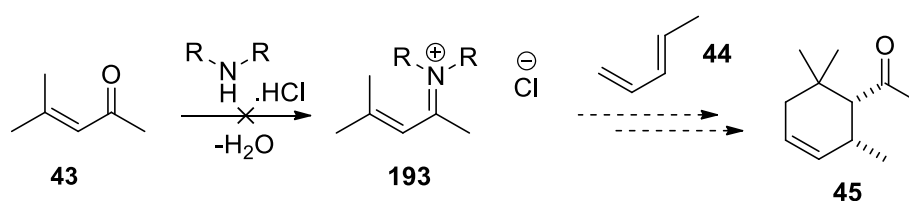


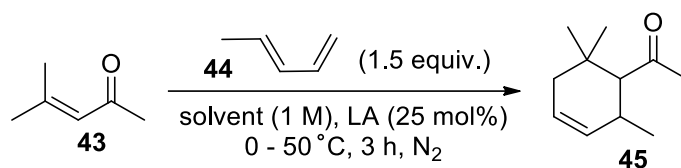
Figure 19: Known Diels-Alder organocatalysts employed for the reaction.



Scheme 37: Proposed disfavoured iminium formation of mesityl oxide and secondary amines.

2.2.2. Lewis Acid Approaches

A range of Lewis acids (LAs) were next screened as promoters of the reaction (Table 12). The reactions were conducted on a 1 mmol scale with 1.5 equivalents of (*E*)-piperylene and 25 mol% of the LA in either toluene or THF (1 M), conversion was estimated by GC-MS analysis using *n*-pentadecane as an internal standard. In all cases the attempted reactions in THF yielded no product. None of the 16 catalysts tested gave conversions close to those achieved with $AlCl_3$ (26%). In the case of lower yielding LAs, diene polymerisation was still problematic, meaning that simply leaving the reaction for longer reaction periods was not an option.

Table 12: Lewis acid screen for the Diels-Alder reaction of mesityl oxide and piperylene.

Entry	Lewis acid	Solvent	GC Conversion (%) ^a
1	AlCl ₃	toluene	26
3	BF ₃ ·OEt ₂	toluene	0
5	Sc(OTf) ₃	toluene	0
7	La(OTf) ₃	toluene	3
9	FeCl ₃	toluene	0
11	Bi(OTf) ₃	toluene	4
13	Cu(OAc) ₂	toluene	0
15	Cu(OTf) ₂	toluene	<1
17	AgNO ₃	toluene	0
19	Fe(OAc) ₂	toluene	0
21	FeSO ₄ ·7H ₂ O	toluene	0
23	CoCl ₂	toluene	0
25	12WO ₃ ·H ₃ PO ₄ ·xH ₂ O	toluene	3
27	ZnI ₂	toluene	0
29	ZnBr ₂	toluene	0
31	MgCl ₂	toluene	0

Reactions conducted on a 1 mmol scale. ^aConversion calculated using *n*-pentadecane as an internal GC standard.

Electing to proceed with AlCl₃, we attempted to lower the AlCl₃ loading using an AlCl₃·2THF adduct. This has been reported in the literature to act as a slightly less acidic alternative to AlCl₃.¹⁰⁶ Lewis acids such as AlCl₃ are known to promote the polymerisation of dienes.¹⁰⁷ It was therefore speculated this may result in reduced levels of diene polymerisation, allowing for fewer equivalents of the diene and Lewis acid to be used.

The aluminium-THF adduct was therefore prepared and employed in the DA reaction at various loadings being compared directly with the use of AlCl₃ alone (Figure 20 and 21). Both reactions were conducted under solvent free conditions (SFC). Conversions were again calculated using GC-MS with *n*-pentadecane as the internal standard. Generally the yield observed was lower

with the THF adduct, this would suggest that the Lewis acidity of the aluminium was lowered but that the effect this had on diene polymerisation was negligible with respect to the outcome of the reaction. The decreased yields can therefore be seen as a direct effect of decreased catalyst activity.

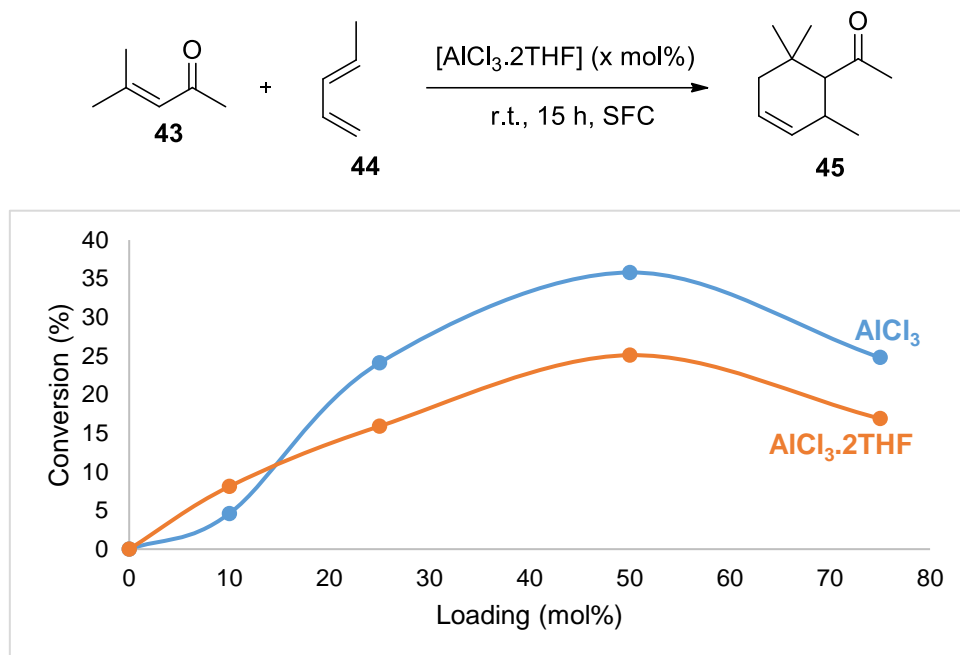


Figure 20: Yield vs. aluminium complex loading at r.t. after 15 hours.

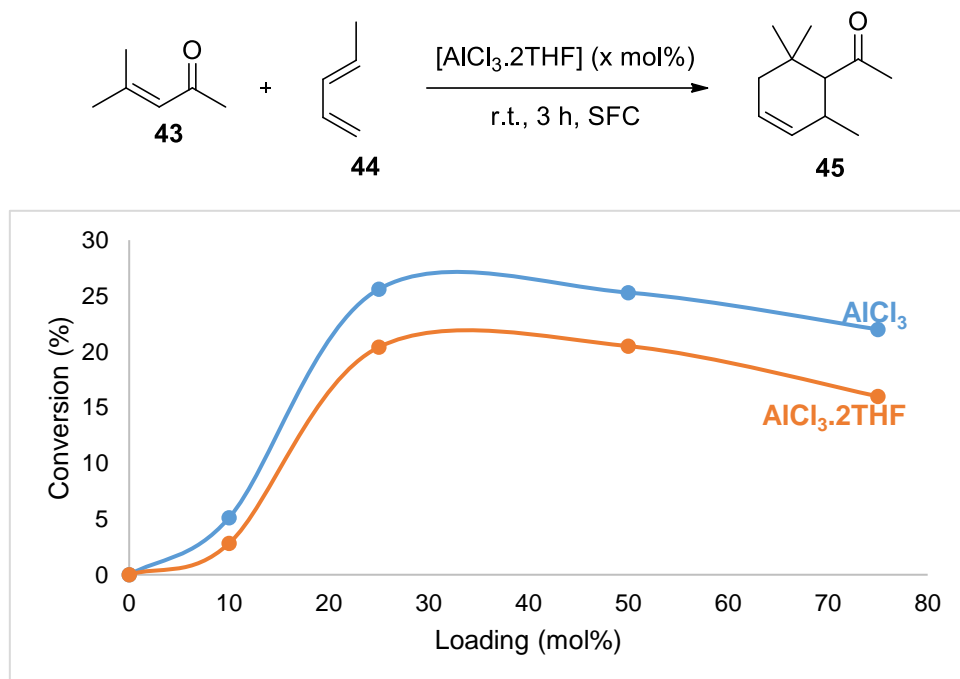


Figure 21: Yield vs. aluminium complex loading at 50 °C after 3 hours.

The assumption that diene polymerisation plays a key role in determining the outcome of the reaction was further studied (Figure 22). Two parallel reactions were set up simulating the industrial scale procedure on a 20 mmol scale. To one of the reactions, the diene was added over a period of 5 minutes and to the other, the diene was added in three portions over three hours (one third of the total amount every hour).

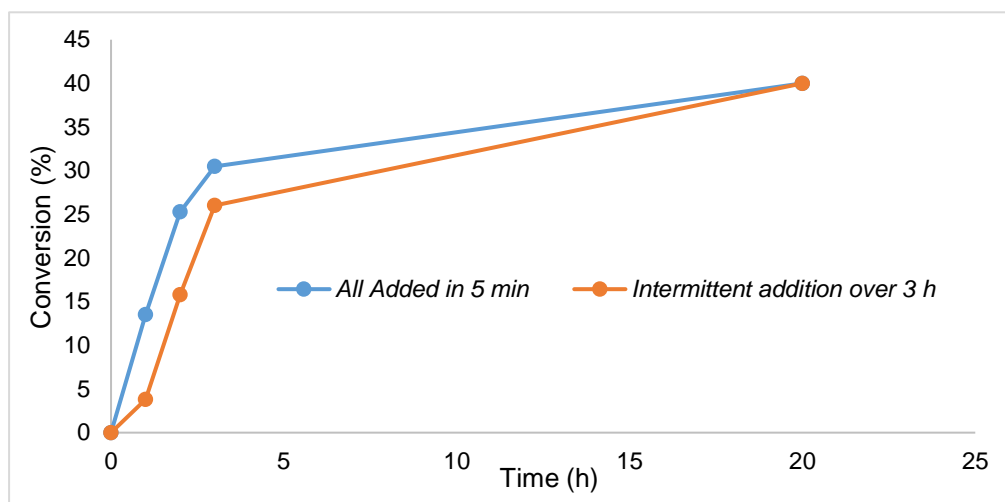


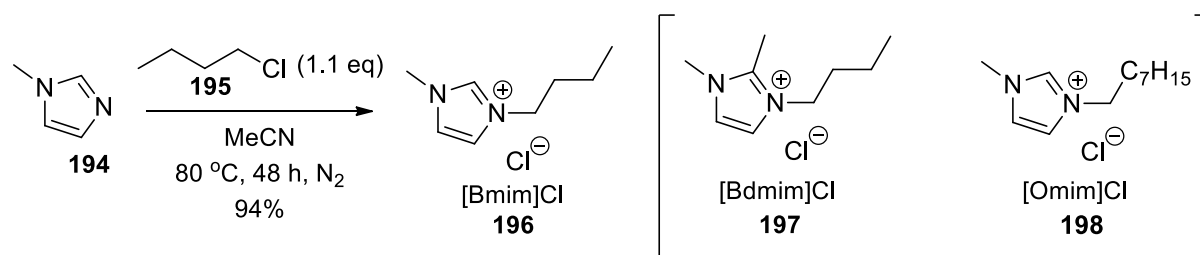
Figure 22: Effect of diene addition rate on yield (65 mol% AlCl_3).

Slower addition of the diene clearly resulted in slower product formation—this was to be expected—however, the yields after 20 hours of stirring at room temperature were identical. This would suggest that, as long as the mixture is kept below the temperature at which polymerisation becomes runaway, *ca.* 40 °C, the impact of the polymerisation is negligible with regards to the final outcome of the reaction. Efforts in terms of optimisation/cost reduction should indeed therefore be geared towards catalysis.

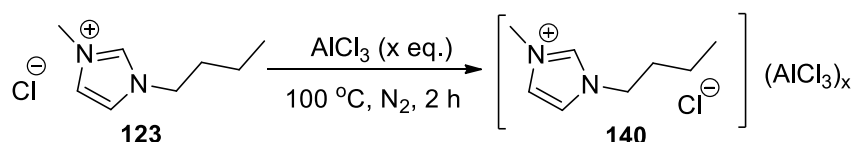
2.2.3. Chloroaluminate Ionic Liquids

Ionic liquids (ILs) have attracted much attention lately as green solvents with the potential for recyclability.¹⁰⁸ ILs have also been used in conjunction with Lewis acids to form metal complexes which have in turn been used to catalyse DA reactions.¹⁰⁹ This combination offers the potential for recycling and reuse of the Lewis acid.¹¹⁰ The so called ‘chloroaluminate’ ionic liquids (CILs),¹¹¹ are comprised of AlCl_3 complexed in various ratios with ionic liquids. These were investigated as solvents/catalysts for the DA reaction.

Commercially available 1-octyl-3-methylimidazolium (Omim) chloride **198** was used to prepare a range of zinc, iron and aluminium salts (Table 13). Similarly, 1-butyl-3-methylimidazolium (Bmim) **196** and 1-butyl-2,3-dimethylimidazolium (Bdmim) **197** salts were prepared according to Scheme 38. A series of chloroaluminate salts were subsequently prepared according to Scheme 39 under anhydrous conditions.



Scheme 38: Preparation of ionic liquids.



Scheme 39: Preparation of chloroaluminate salts.

Table 13: Chloroaluminate ionic liquid screening.

CC(=O)C=C.C=C=C>>CC(=O)C1C=CC(C)CC1

43 + **44** $\xrightarrow[40\text{ }^{\circ}\text{C, N}_2]{[\text{IL}]\text{Cl}(\text{MX}_n)_x \text{ (1 equiv.)}}$ **45**

Entry	Catalyst	Time (h)	Yield (%)
1	[Omim]ZnCl ₂	1	0
2	[Omim]ZnCl ₂	24	0
3	[Omim]Cl(ZnCl ₂) ₂	1	0
4	[Omim]Cl(ZnCl ₂) ₂	24	0
5	[Omim]Cl(ZnCl ₂) _{1.5}	72	<1
6	[Bmim]Cl(ZnCl ₂) _{1.5}	72	<1
7	[Omim]FeCl ₄	18	0
8	[Omim]AlCl ₄	18	0
9	[Omim]Cl(AlCl ₃) ₂	1	5
10	[Omim]Cl(AlCl ₃) ₂	24	27
11	[Omim]Cl(AlCl ₃) ₃	1	<1
12	[Omim]Cl(AlCl ₃) ₃	24	6
13	[Omim]Cl(AlCl ₃) _{1.5}	1	28
14	[Omim]Cl(AlCl ₃) _{1.5}	24	36
15	[Omim]Cl(AlCl ₃) _{1.75}	1	20
16	[Omim]Cl(AlCl ₃) _{1.75}	24	25
17	[Bmim]Cl(AlCl ₃) _{1.5}	18	46
18	[Bdmim]Cl(AlCl ₃) _{1.5}	18	45

Reactions conducted on a 1-3 mmol scale. ^a Yield calculated using n-pentadecane as an internal GC standard.

The salts were then employed stoichiometrically as catalysts for the DA reactions, which were conducted at a 1 – 3 mmol scale under anhydrous conditions. From the results obtained, the optimum ratio of AlCl₃ to IL with the Omim salt was found to be 1.5:1 (AlCl₃:IL) which resulted in a conversion of 36%. Using the equivalent Bmim salt proved to be the more

effective, giving a 46% conversion (GC) after 18 hours. However, recovery of the chloroaluminate salts proved very difficult. A thick brown residue remained at the end of the reaction which had to be washed with water in order to permit isolation of the product by extraction. At this point the metal ionic liquid decomposed due to its moisture sensitivity.

2.2.4. Summary and Conclusion

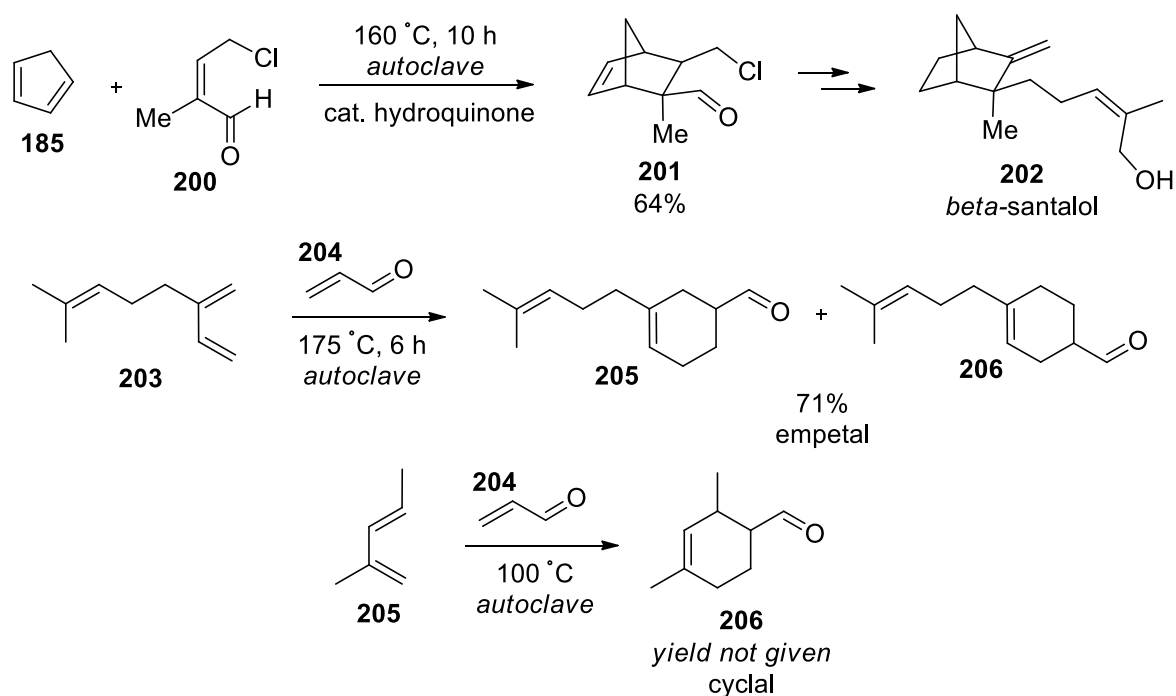
The Diels-Alder process was optimised by IFF for use on a large scale prior to this work. The above studies would suggest that the key to this process lies in the AlCl_3 and improving upon the yield of the current process without using some form of AlCl_3 will be very difficult. The fact that such high loadings (65 mol%) of insoluble AlCl_3 are required for a yield of 64% means that making this into a reasonable flow process will also be very difficult.

2.2.5. Diels-Alder Reactions and Flow Chemistry

Although the processing of slurries in flow has been made possible by the incorporation of ultrasound¹¹² and technologies such as the Coflore ACR,^{19, 86} the potential gains are not outweighed by the complications that will arise when taking the above DA reaction into flow. Such a process involving an aluminium slurry would require extraneous processing aids in flow. Also, the liquid-liquid extraction used gives poor phase separation and so a batch-wise extraction process would still be necessary.

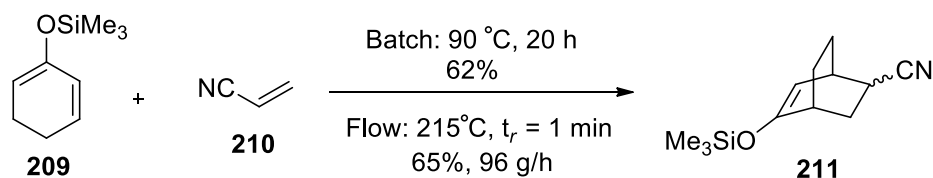
In terms of translating DA reactions to flow, the focus should therefore be on the development of reactions involving homogenous catalysis or thermally driven processes. Examples of thermal DA reactions used in the flavour and fragrance industry are shown in Scheme 40. There are clear processing benefits to be leveraged by conducting thermal DA reactions in flow such

as more efficient heat transfer, superior temperature control, improved reaction kinetics and safety implications with regards to handling and transport.



Scheme 40: Examples of thermal DA reactions used in flavours and fragrances.

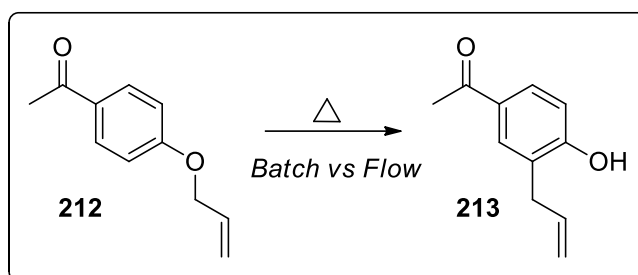
Such advantages have been demonstrated for a range of thermal DA and rearrangement reactions as reported in the literature. Specifically, in 2012 Abele *et al.* reported the Diels-Alder reaction of (cyclohexa-1,5-dien-1-yloxy)trimethylsilane **209** with both α -acetoxyacrylonitrile and acrylonitrile **210** in flow (Scheme 41).¹¹³ Batch to flow comparisons revealed that overcoming thermokinetic issues associated with batch scale-ups was possible by adopting a flow approach. For the processing of acrylonitrile **210**, access to a much larger temperature window (<215 °C compared to <90 °C) in flow allowed for far more rapid cycloaddition. Using a residence time of only 1 minute (vs. reaction time of 20 h in batch at 90 °C) in flow with a simple stainless steel tube reactor resulted in superior yields compared to the batch process. In a similar report by Kappe in 2010 the kinetics of the DA reaction of 2,3-dimethylbutadiene with acrylonitrile could also be improved markedly by adopting a flow approach.¹¹⁴



Scheme 41: Batch vs. flow for the Diels-Alder reaction of (cyclohexa-1,5-dien-1-yloxy)trimethylsilane **209** with acrylonitrile **210**.

Claisen rearrangements in flow have also been extensively studied.¹¹⁵⁻¹¹⁹ In 2011 scientists at Eli Lilly compared the thermal *ortho*-Claisen rearrangement of the allyl ether **212** (Table 14), an important early phase intermediate, in flow and batch.¹¹⁹ Significant advantages were associated with the flow protocol, stemming from the ability to safely use higher concentrations (and therefore less solvent), pressures and temperatures. The result of moving to a flow regime was a much safer, highly reproducible system which was easier to heat to the required temperature. A continuous microwave reactor process was also developed for high temperature and high pressure Claisen rearrangements in 2014.¹¹⁵ In 2015, a continuous method for preparing ocimene from thermo isomeric alpha-pinene in the liquid phase was patented by Jiangxi Jiayuan Fragrance Co. Ltd¹²⁰ indicating industrial interest in this area. There are likely many more isomerisation or rearrangement reactions for which a flow approach could prove beneficial. This should be an area of focus with regards to future work on the application of flow chemistry to the flavour and fragrance industry.

Table 14: Batch vs. flow for the thermal Claisen rearrangement of allyl ether **212**.



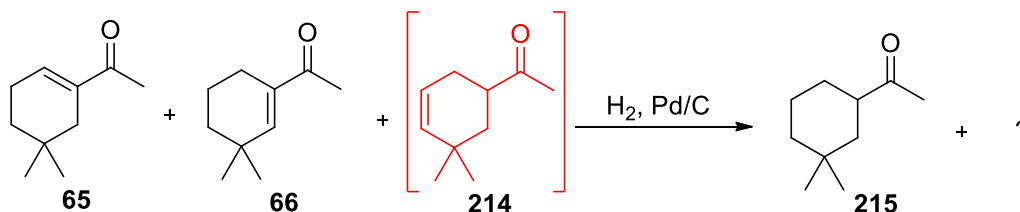
	<i>Batch Process</i>	<i>Flow Process</i>
Solvent	Diphenyl ether	<i>N</i> -methyl pyrrolidinone
Concentration	33 wt%	50 wt%
Temperature	220 °C	230 °C
Solvent b.p.	259 °C	202-204 °C
Operating pressure	1 bar	15 bar
Reaction time	5 h	4 h
Workup	Crystallisation on cooling (potential to freeze solvent below 27 °C)	Aqueous down out and extraction
Safety	Potential for runaway reaction	Improved heat transfer provides better temperature control; contained system; potential to safely run at higher concentrations
Manufacturability	220 °C not easily reached by typical batch reactor heat transfer systems	230 °C easily reached in ovens
Robustness	Reaction temperature variations leading to variation in yields and purity	Highly reproducible

2.3. Galbascone

2.3.1. Mechanistic Studies of the Acid-Catalysed Cyclisation of Enynes 62-64

2.3.1.1. Identification of Third Product of Enyne Cyclisation

The initial aim of this research was to better understand the current rearrangement/cyclisation process used in the industrial synthesis of α -dehydroherbac **65**, a precursor to Galbascone (Scheme 9). The process used gives rise to three products, two of which were known, **65** and **66**. Hydrogenation (H-Cube, full H₂ mode, 40 °C, 0.2 M in EtOH) of a mixture of the three products (Scheme 42) afforded the expected saturated analogue **215** as well as a second product, suggesting that the third product was not simply a double bond isomer such as **214**.



Scheme 42: Hydrogenation of enyne cyclisation product mixture (**62-64**).

Complete separation of the products was not possible either by column chromatography or distillation so the ¹H-NMR spectrum of a sample containing exclusively α - and β -dehydroherbac was compared to the spectrum of the mixture to obtain a ‘subtracted’ spectrum relating to the third product (Figure 24).

Following 2-D NMR experiments (COSY, HMBC, HSQC) and Pureshift ¹H NMR,¹²¹ the third product was assigned as the unsaturated cycloheptanone derivative, dihydroeucarvone **216**, peak numbers correspond to protons in Figure 24. This structure was consistent with analytical data from the literature.¹²²

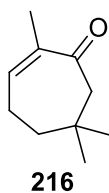


Figure 23: Dihydroeucarvone.

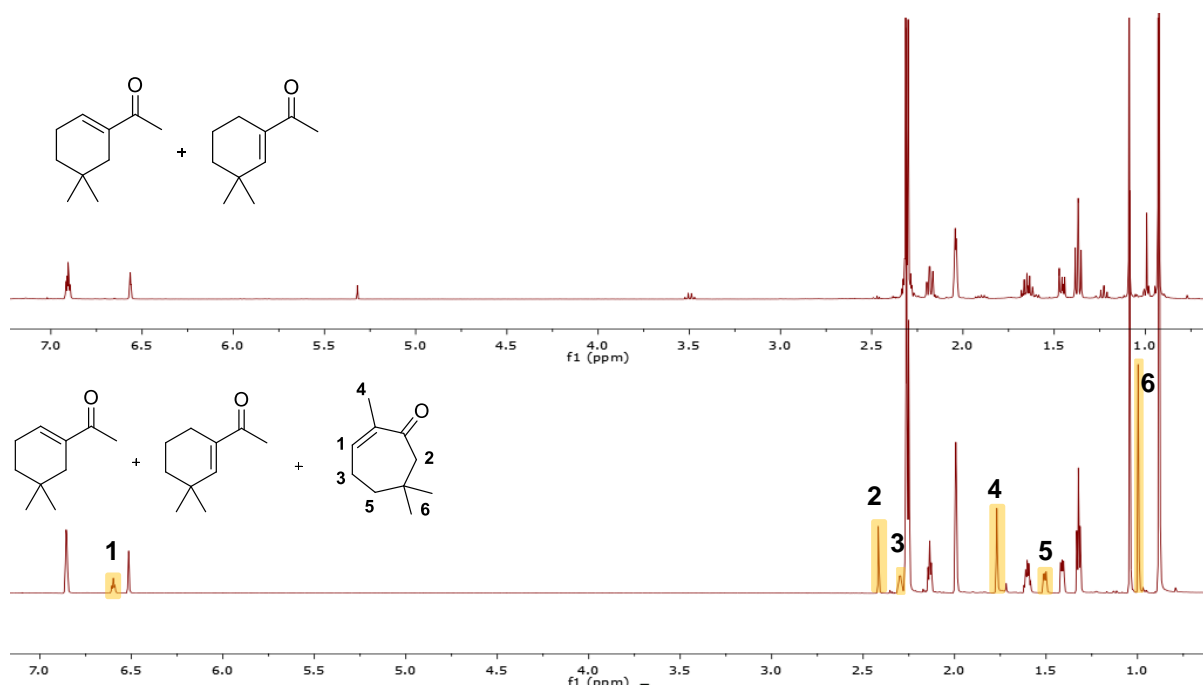
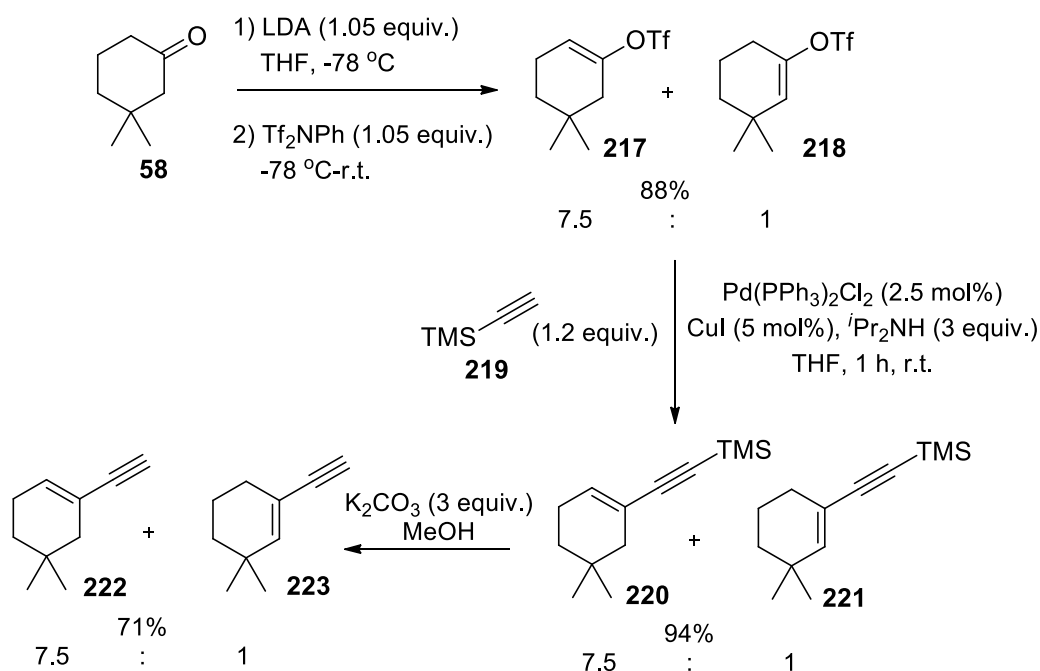


Figure 24: Stacked ^1H -NMR spectra of different product mixtures (dihydroeucarvone peaks highlighted).

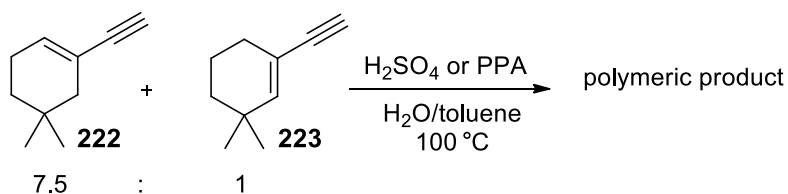
2.3.1.2. Synthesis of Potential Cyclic Cyclisation Process Intermediates

The mechanism for the formation of **65**, **66** and **216** was thought to involve two separate processes – cyclisation and acetylene hydrolysis, though it was not clear in which order these occurred. Several potential intermediates were therefore synthesised and subjected to the process conditions in order to assess this sequence. The first target structure, 1-ethynyl-5,5-dimethylcyclohex-1-ene **222** was prepared in three steps according to Scheme 44. Triflation of 3,3-dimethylcyclohexanone **58** under kinetic control afforded a 7.5:1 mixture of the enol triflate isomers **217** and **218** in 88% yield. The use of triflic anhydride here was unsuccessful, however, the milder triflating agent, *N*-phenyl-bis-(trifluoromethanesulfonimide), allowed high yield. The product was then subjected to a Sonogashira coupling with trimethylsilyl acetylene to give the TMS protected enynes **220** and **221** with conservation of the isomeric ratio. Desilylation of these intermediate gave the cyclic enynes **222** and **223** which were

hydrolysed using polyphosphoric acid and sulfuric acid in water/toluene under analogous conditions to the IFF process (Scheme 9).

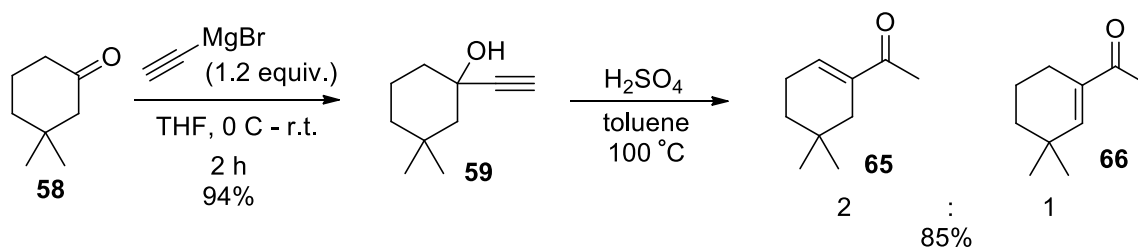


Scheme 43: Synthesis of 1-ethynyl-5,5-dimethylcyclohex-1-ene **222**.



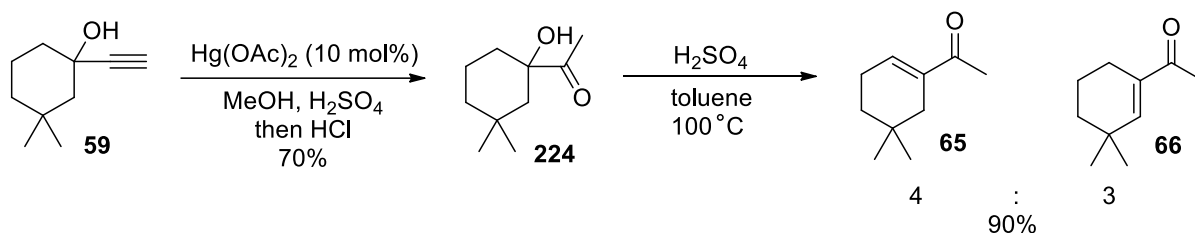
Scheme 44: Cyclic enyne acidification.

In all cases, under these acidic conditions, a polymeric product was returned suggesting that either **222** is not involved as an intermediate or that it forms and simply contributes towards the polymerisation that is known to occur during the process.



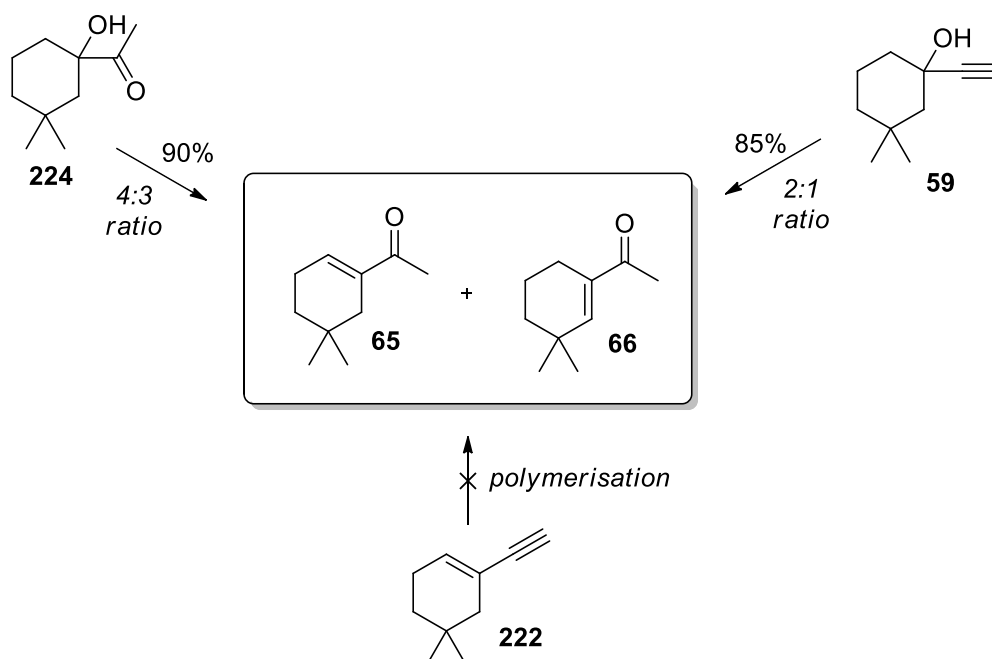
Scheme 45: Synthesis of 1-ethynyl-3,3-dimethylcyclohexanol **59**.

Next, the alcohol, 1-ethynyl-3,3-dimethylcyclohexanol **59** was prepared in a single step from 3,3-dimethylcyclohexanone **58** and ethynylmagnesium bromide in 94% yield (Scheme 45). The resultant propargylic alcohol gave α - and β -dehydroherbac upon acidification with sulfuric acid in a 2:1 ratio respectively, in an 85% yield and no dihydroeucarvone formation was observed. **59** can therefore be considered as a plausible intermediate in the IFF process.



Scheme 46: Synthesis of 1-(1-hydroxy-3,3-dimethylcyclohexyl)ethanone **224**.

The keto derivative, 1-(1-hydroxy-3,3-dimethylcyclohexyl)ethanone **224** was also prepared *via* oxymercuration of the propargylic alcohol **59** (Scheme 46). When subjected to acidification, this compound also gave rise to a mixture of α - and β -dehydroherbac but this time in a 4:3 ratio respectively. Again, no dihydroeucarvone was formed, reinforcing its assignment as the proposed seven-membered ring species.

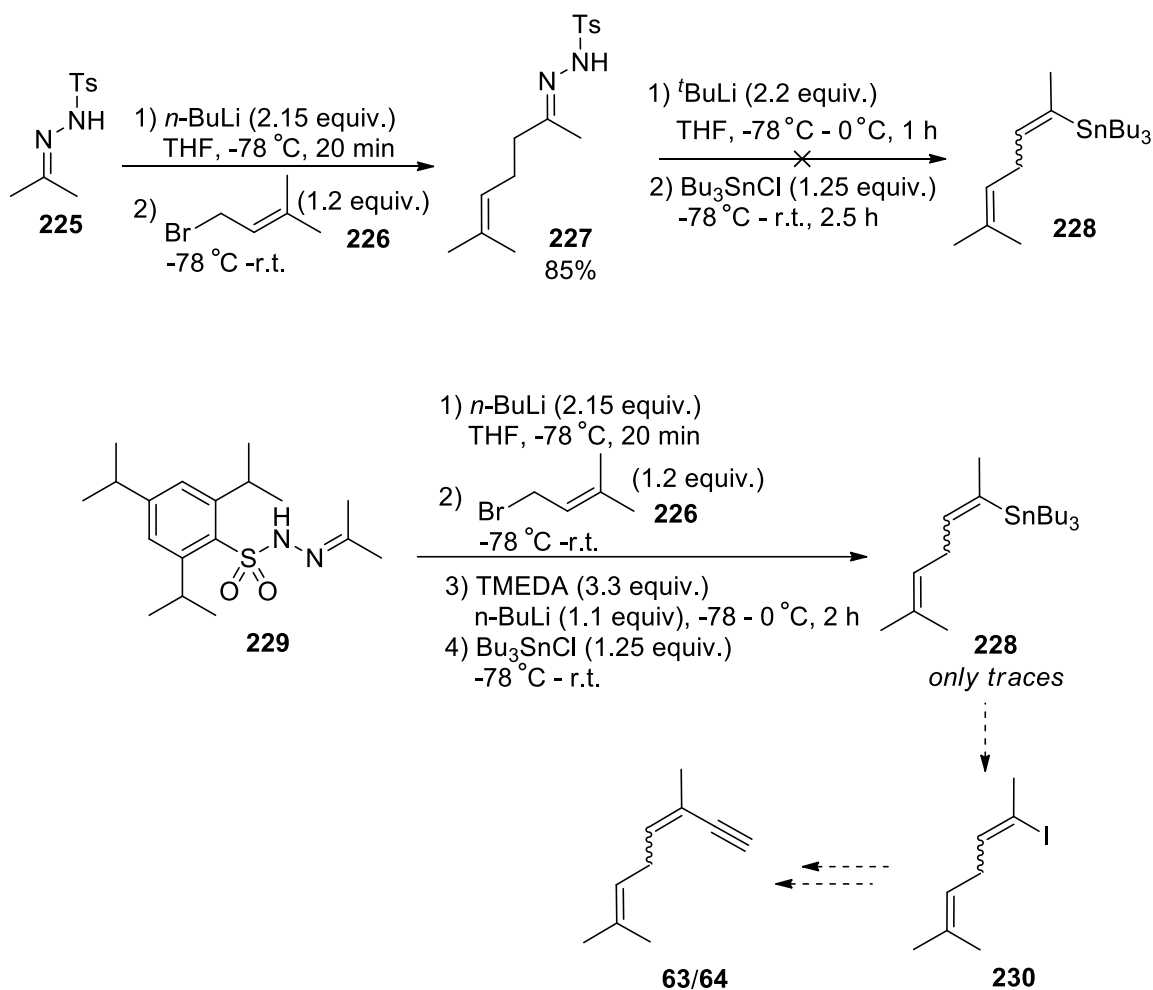


Scheme 47: Overview of species prepared.

2.3.1.3. Synthesis of an Endo-Enhanced Acyclic Enyne Mixture

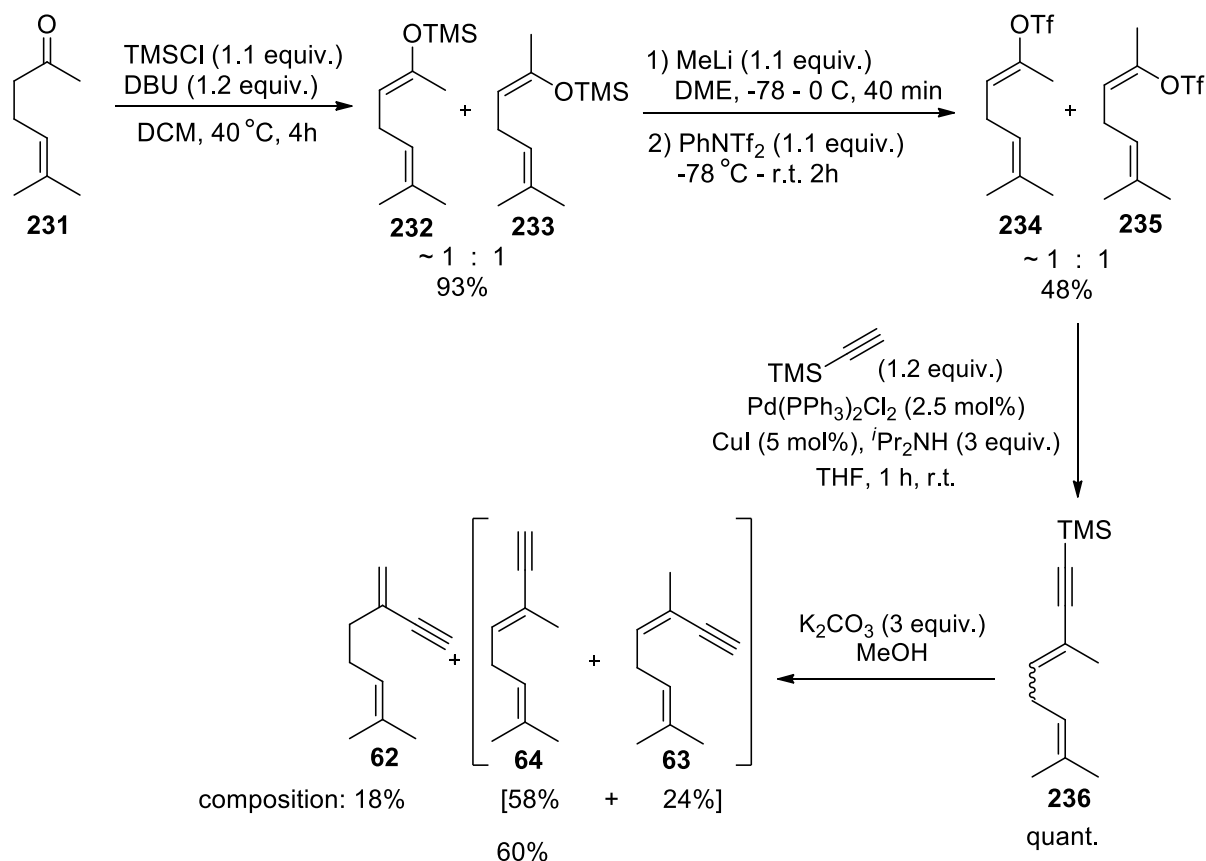
We aimed initially to prepare isomerically pure sample of each of the enyne dehydration products **62**, **63** and **64**, however, only enhanced mixtures could be obtained due to isomerisation during their synthesis. Also, a synthesis which differentiated the *E*- and *Z*-endo-isomers was not achieved under the conditions tested.

Initially, a route based upon a Shapiro reaction towards the iodo compound **230** was explored¹²³ as this would allow for subsequent Sonogashira coupling with trimethylsilyl acetylene. The Shapiro reaction of tosyl hydrazone **227** was, however, unsuccessful with regards to formation of the tributyltin compound **228** under all conditions tested (Scheme 48).



Scheme 48: Attempted Shapiro routes towards tin compound **228**.

In each case the hydrazone starting material **227** could be partially recovered, it was therefore speculated that a bulkier tosyl group would aid in the loss of N₂ as required by the desired reaction, so the triisopropylphenyl derivative **229** was also prepared and tested. This however only gave the tributyltin product in trace amounts.



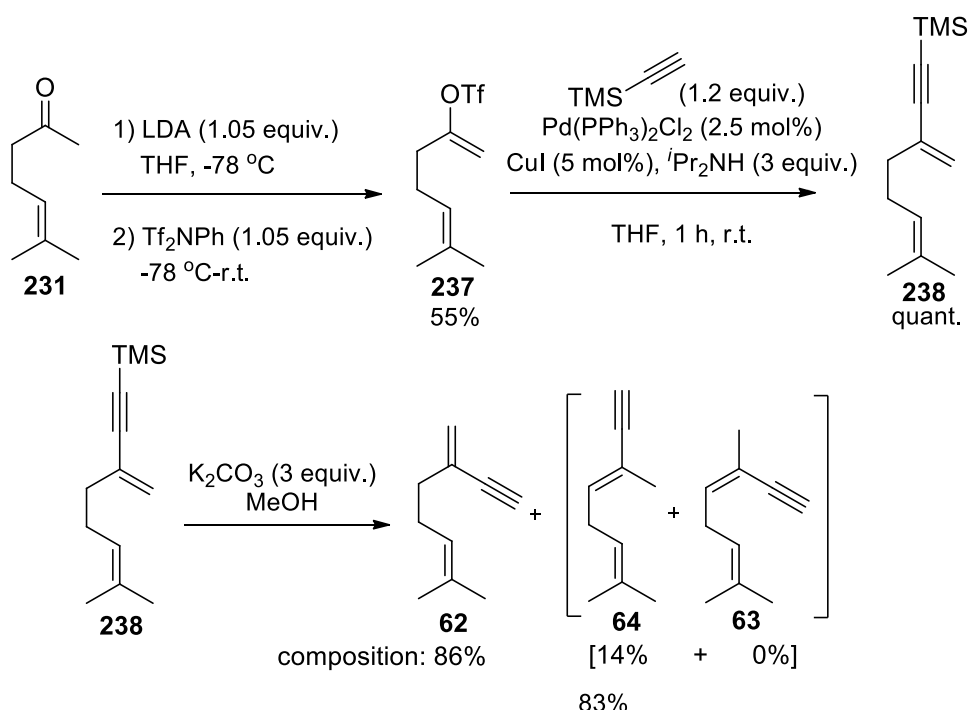
Scheme 49: Successful route towards an *endo*-enhanced acyclic enyne mixture.

Alternatively we considered forming the TMS-enolates **232** and **233** under thermodynamic conditions and converting these to the enol triflates **234** and **235** allowing the possibility of once again coupling with TMS-acetylene (Scheme 49). Under classical thermodynamic conditions the TMS-enolates **232** and **233** were obtained in a 1:1 ratio in good yield. As previously experienced, the use of triflic anhydride in the subsequent step was unsuccessful, but employing the triflimide gave the corresponding enol-triflates **234** and **235** in a 1:1 ratio and a 48% yield. After coupling and desilylation, a mixture containing predominantly the *endo*-isomers was obtained, the presence of *exo*-isomer **62** could be traced back to the initial TMS-

enolate formation and made up 18% of the final composition. $^1\text{H-NMR}$ was used to determine isomer compositions, however, NOESY did not allow for distinction between the two *endo*-isomers **64** and **65**. Composition values quoted from here onward therefore do not specify between *endo*-isomers **64** and **65**.

2.3.1.4. Synthesis of an *Exo-Enhanced* Acyclic Enyne Mixture

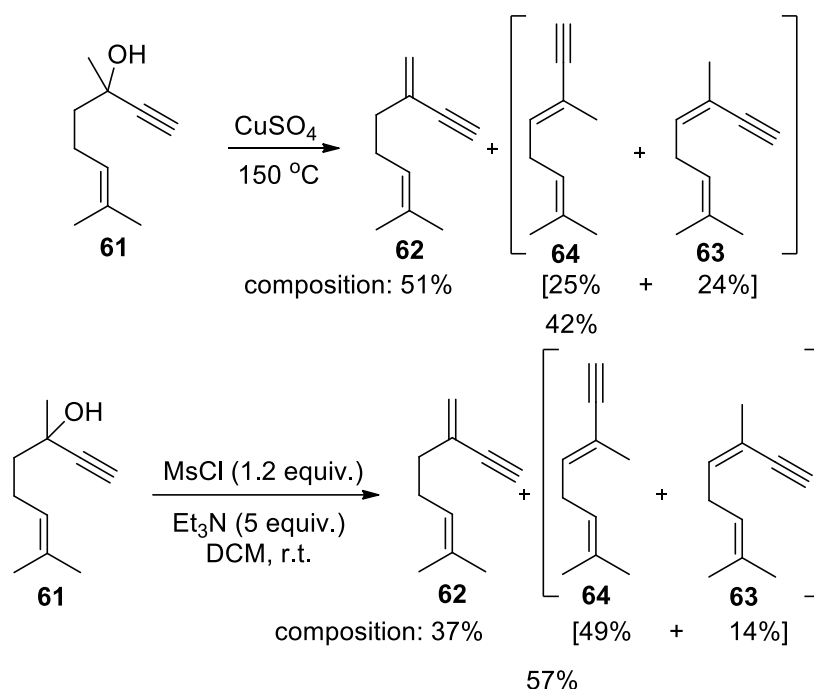
The synthesis of an *exo*-enhanced mixture of isomers was carried out in an analogous manner to the route employed for the synthesis of 1-ethynyl-5,5-dimethylcyclohex-1-ene **222**. Kinetic enol-triflate formation was followed by TMS-acetylene coupling and desilylation to furnish a mixture containing 86% of the *exo*-isomer (Scheme 50), the presence of one of the *endo*-isomers was traced back to the initial enol-triflate formation and accounted for 14% of the final composition.



Scheme 50: Successful route towards an *exo*-enhanced acyclic enyne mixture.

2.3.1.5. Other Mixtures Obtained

A sample from the IFF process (dehydration of dehydrolinalool) was obtained, this contained an almost equal quantity of *exo*- and *endo*-isomers (51% *exo*, 49% *endo*). A further sample containing 37% *exo* and 63% *endo* (49% and 14%), was obtained by mesylation and *in-situ* elimination of dehydrolinalool (Scheme 51).



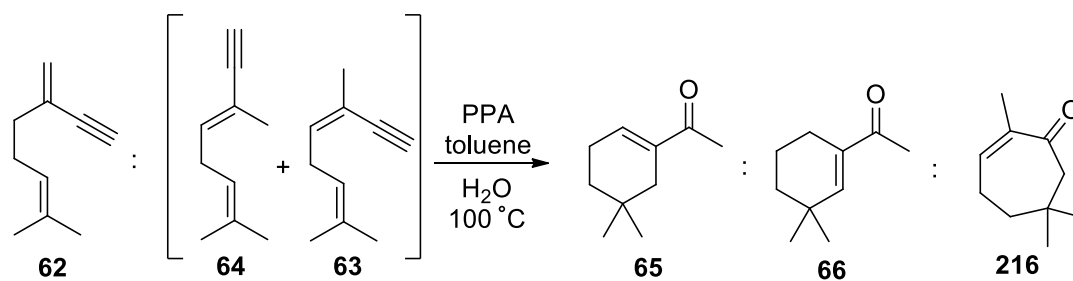
Scheme 51: Acyclic mixtures obtained from the IFF process and mesylation-elimination of dehydrolinalool.

2.3.1.6. Subjecting the Isomer Mixtures to Process Conditions

The four mixtures were each subjected to a standard set of conditions that were previously optimised to be representative of IFF's large scale process (0.60 g PPA, 0.75 mL H_2O , 20 mL toluene per gram of starting material). The pH profile for the reaction is very sensitive. The reaction is highly susceptible to polymerisation if the acidity is too high but if the medium is not acidic enough, the reaction simply does not occur. The reactions were conducted on sub-1 mmol scales due to the small quantities of material obtained for the *exo*- and *endo*-enhanced

mixtures (Table 15). By conducting a theoretical mechanistic evaluation, it can be proposed that the *exo*-isomer **62** is the one that gives rise to the 6-membered ring products (Scheme 52). The results seem to validate this, as generally speaking, a higher *exo*-starting material composition translates to a higher α -product composition. Similarly, there is a correlation between the *endo*-starting material composition and dihydroeucarvone **216** product composition validating the proposed enolate mechanism of formation of dihydroeucarvone from enyne **63** as shown in Scheme 52.

Table 15: The outcomes of the cyclisation of a variety of starting material compositions under standard conditions representative of IFF's process.

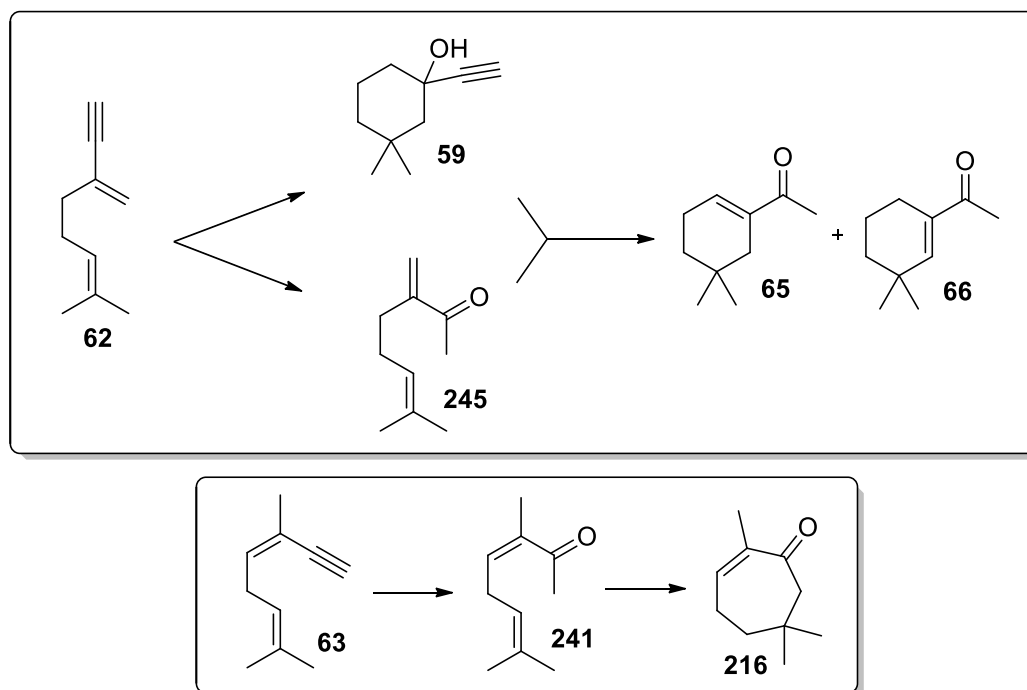


Entry	Sample	Exo	Endo (5.70 ppm)	Endo (5.93 ppm)	α (65)	β (66)	7-c (216)
1	IFF process	51%	25%	24%	52%	28%	20%
2	<i>Exo</i> enhanced.	86%	0%	14%	62%	24%	14%
3	<i>Endo</i> enhanced	18%	58%	24%	27%	9%	64%
4	Mesylation	37%	49%	14%	33%	14%	52%
5	Standardised ^a	51%	25%	24%	22% ^b	10% ^b	10% ^b

Reactions performed on <1 mmol scale. ^a Reaction performed using 1,4-dichloro-2-nitrobenzene as an internal ¹H-NMR standard. ^b Estimated ¹H-NMR yield.

A simple mechanism cannot, however, be imagined for the formation of either of the three products from enyne **64**. Due to the double bond's *endo-E*-geometry, this intermediate is not

set up for a ring formation that would lead to any of the known products (**65**, **66** or **216**). This enyne therefore, either simply contributes to the polymerisation that is known to occur, or may also isomerise to a reactive enyne **62** or **63** under the acidic conditions. This isomerisation would be facilitated by the ability to form a tertiary carbocation at the relevant carbon (C-6). The results in Table 15 indicate that isomerisation does indeed occur to some extent during the process. By considering Table 15, entry 2 alone, it would seem that the *endo* isomer at 5.93 ppm in the $^1\text{H-NMR}$ (*endo*-5.93) gives quantitative dihydroeucarvone as the *endo*-5.93 composition in the starting material is equal to the **216** (7-*c*) content in the product. However, in entry 3, this same enyne comprises only 24% of the starting material mixture, yet the product is composed of 64% 7-*c* contradicting this. Also, the fact that in entry 4, a product composed of 52% 7-*c* is obtained from a starting material comprising 49% *endo*-5.70 and just 14% *endo*-5.93, suggests that both *endo*-isomers contribute to the formation of 7-*c*. It must also be noted, however, that percentages in entry 1-4 represent product composition and not yields.



Scheme 52: Possible formation pathways for the three products.

A plot of starting material *exo*-composition vs. product α -composition (Figure 25) shows positive correlation with more of a logarithmic than linear relationship, this is also indicative of isomerisation. If no isomerisation between intermediates occurred, a linear relationship would be predicted. Table 15, Entry 5 represents a repeat of entry 1 but with an internal ^1H -NMR standard, this allowed for actual quantification of the products and revealed an overall yield of 42%. This is consistent with yields obtained in the IFF process and it is believed that the low yield is attributable to polymerisation of starting material/intermediates.

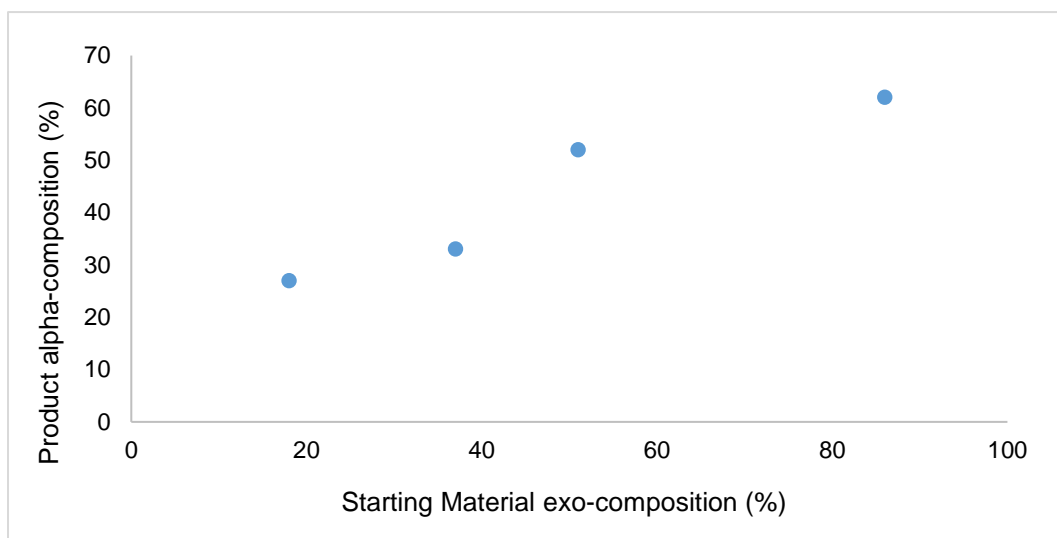
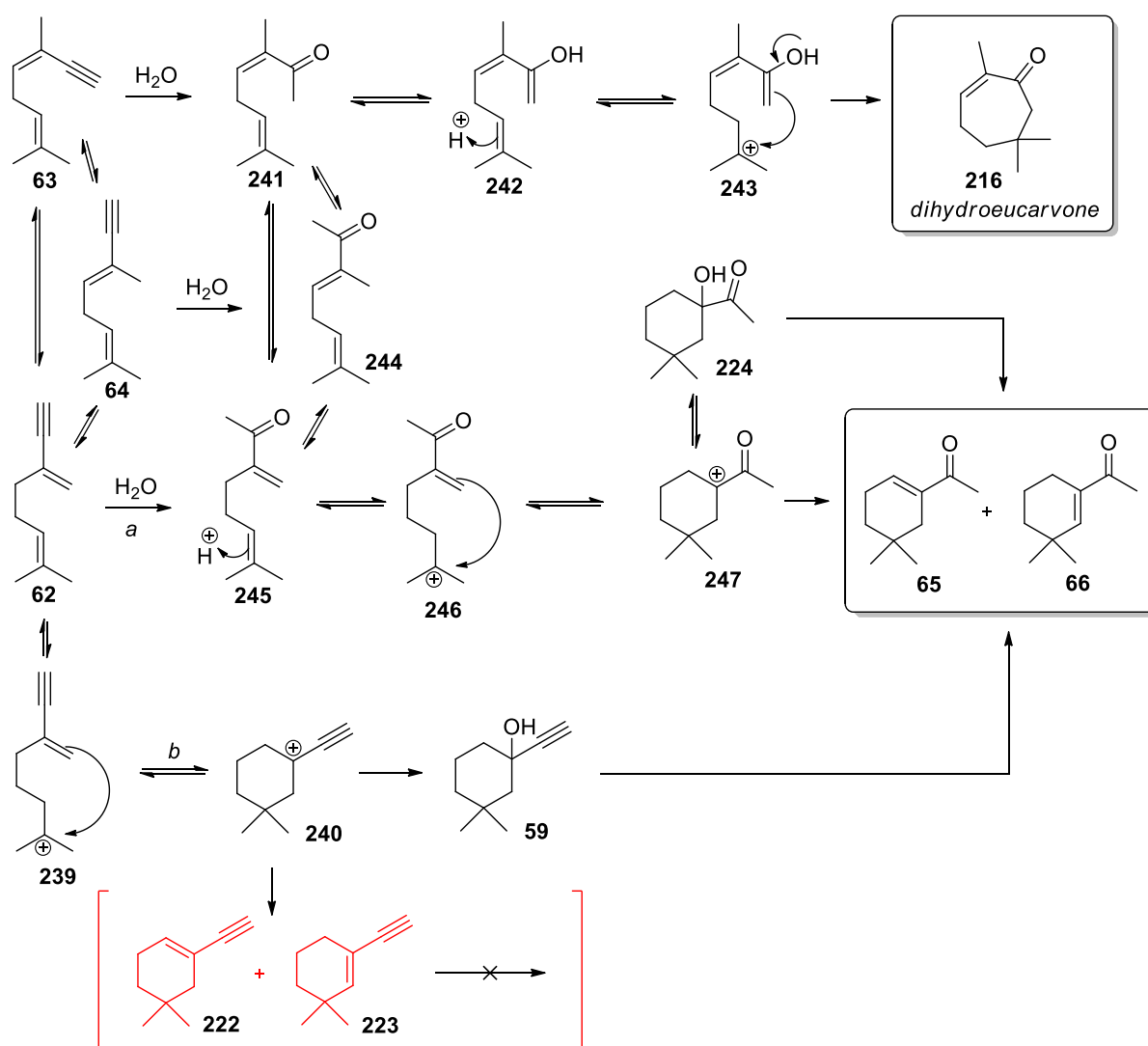


Figure 25: Starting material *exo*-composition vs. product α -composition.



Scheme 53: Mechanistic overview of IFF's dehydroherbac process.

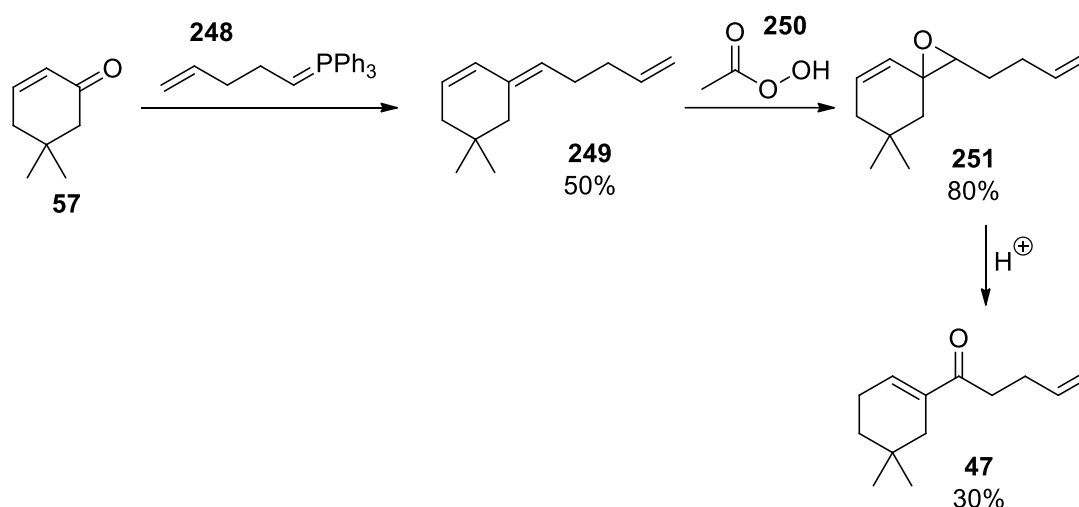
An overall mechanistic interpretation of IFF's process is given in Scheme 53. It is proposed that enyne **63** is responsible for the formation of dihydroeucarvone **216** and follows an enol-driven cyclisation pathway. The fact that dihydroeucarvone forms in the first place suggests that acetylene hydrolysis may occur prior to cyclisation in the case of all enynes. Enyne **62**, therefore may either follow *pathway a* or *pathway b* depending on at which stage the acetylene functionality is hydrolysed. In order to validate *pathway a*, the synthesis of intermediate **245** was briefly considered, however, a reasonable route was not found. The results displayed in Table 15 suggest that isomerisation does occur but only slowly. A clear correlation between

starting material *exo*-composition and product α -composition has been demonstrated, which would indicate that the isomerisation is slow in comparison to the rate of cyclisation. If isomerisation occurred readily and rapidly, this would present itself as a much poorer correlation. In the proposed model, therefore, enyne **62** and **63** either give α/β -dehydroherbac **65/66** or dihydroeucarvone **216**, respectively, or polymerise under the process conditions. Enyne **64** may also simply polymerise or give rise to any of the three products depending on the position of the double bond in its isomerisation product.

In conclusion, the key to enhancing the yield of α -dehydroherbac with this process lies in pushing the *exo*-enyne content of the starting material as high as possible. Even a 100% *exo*-starting material though will not lead to a product comprising exclusively the desired α -dehydroherbac isomer. According to the proposed model it will be very difficult to increase selectivity towards the α - over β -dehydroherbac and the current process has already been optimised with regards to this as well as to maximising the *exo*-content of the dehydration product of the first step.

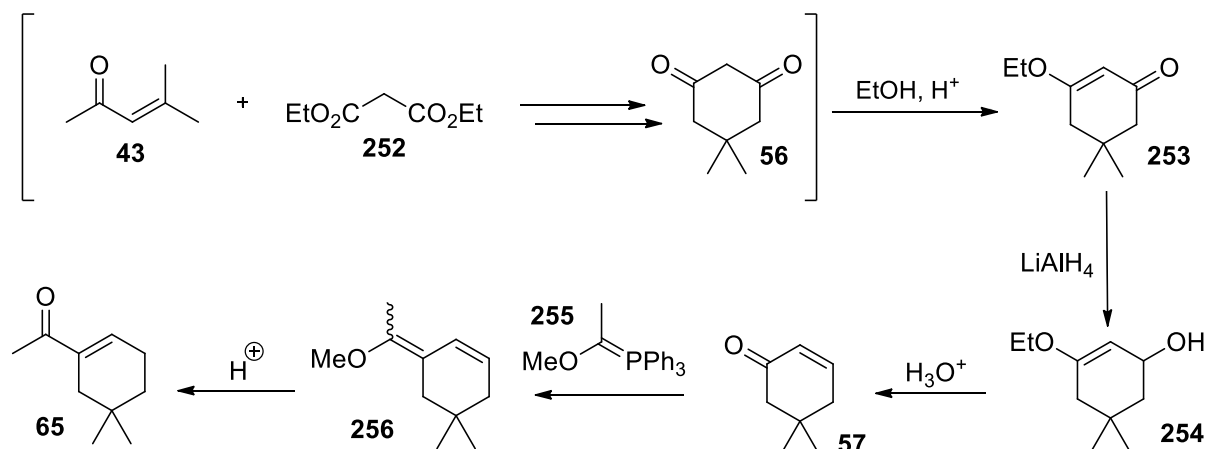
2.3.2. Alternative Synthetic Approaches Towards α -Dehydroherbac – A Wittig Route

Wittig routes have been explored previously within this area. In 1976 a patent was filed disclosing the reaction of 5,5-dimethylcyclohex-2-enone **57** with the Wittig reagent **248**, which after a further two steps gave galbascone with the correct cyclohexenyl double bond geometry (Scheme 54).⁶⁰



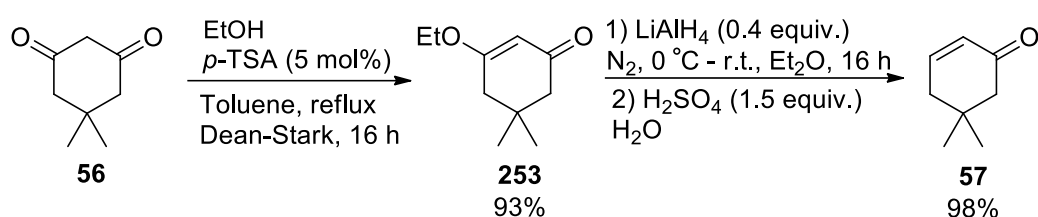
Scheme 54: Previously disclosed Wittig route to galbascone.

To our knowledge, a Wittig route towards α -dehydroherbac, however, has never been reported, the below sequence was therefore proposed (Scheme 55). The route starts from dimedone **56**, which is cheap and easily prepared by treatment of mesityl oxide with diethyl malonate **252**.¹²⁴



Scheme 55: Proposed Wittig route towards α -dehydroherbac.

Forming the enol ether **253** followed by reduction would give access to 5,5-dimethylcyclohex-2-enone **57** which could be intercepted by the Wittig reagent **255**. It was hoped that acidification of the resultant diene would give exclusively α -dehydroherbac due to the diene conjugation. The proposed Wittig reagent was not commercially available, so (methoxymethyl)triphenylphosphonium chloride salt **257** was employed for a preliminary scoping exercise. The preparation of 5,5-dimethylcyclohex-2-enone **57** was performed in 91% yield over the two steps as shown in Scheme 56.



Scheme 56: Preparation of 5,5-dimethylcyclohex-2-enone.

Table 16: Screening of work-up conditions.

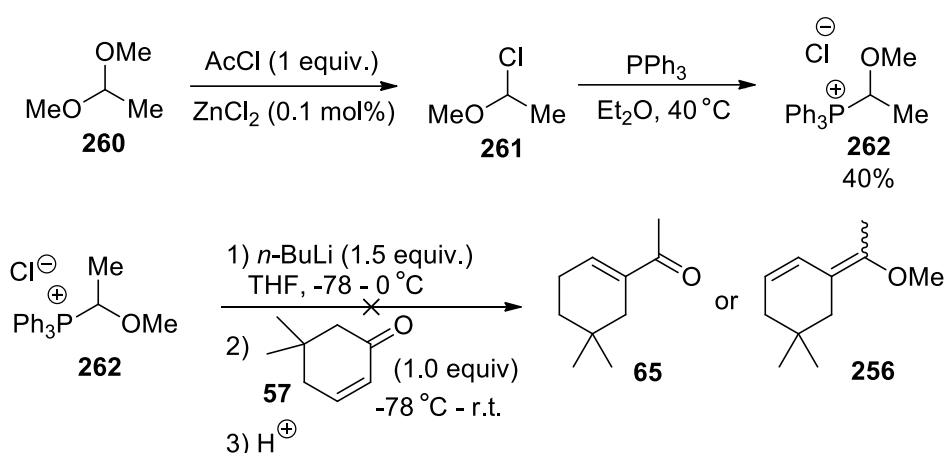
Entry	Work-up H^+ source	1H -NMR yield of 259 ^a
1	1 M HCl	4%
2	Saturated aqueous NH_4Cl	0%
3	SiO_2	0%
4	HCl in Et_2O (2 M)	23%
5	$SiO_2.H_2SO_4$	1%

^a1,3,5-trimethoxybenzene used as an internal 1H -NMR standard. ^bReactions conducted on a 10 mmol scale.

Formation of the diene **258** seemed to proceed smoothly by 1H NMR, however, the subsequent hydrolysis did not. A screening of work-up conditions revealed that the diene intermediate was

sensitive to polymerisation with the best work-up conditions found to be treatment with HCl in diethyl ether (23% ^1H -NMR yield). Under these conditions, the highest isolated yield of the desired α,β -unsaturated aldehyde obtained was 25% after SiO_2 column chromatography. Despite the poor yield, none of the undesired β -product isomer was formed suggesting that preparing exclusively α -dehydroherbac would indeed be potentially possible using this methodology.

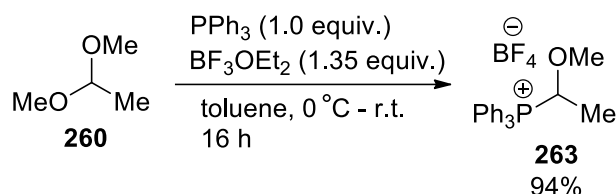
Since the relevant Wittig salt was not commercially available, we next sought a method of preparing it. The chloride salt **262** was prepared from 1,1-dimethoxy ethane **260** in 40% in a two-step one pot procedure adapted from the literature¹²⁵ (Scheme 57).



Scheme 57: Preparation and use of (1-methoxyethyl)triphenylphosphonium chloride **262**.

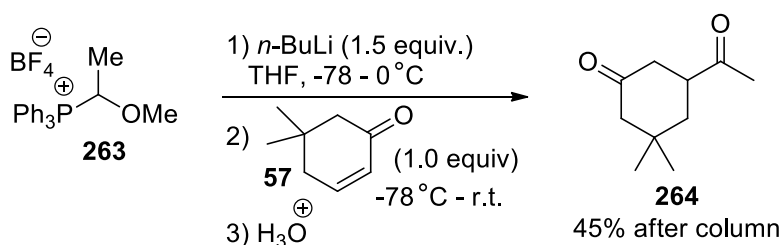
However, when subjected to the reaction conditions as established in Table 16, the chloride salt **262** gave neither of the two products **65** or **256** shown in Scheme 57 with starting material **57** being mostly recovered. Upon deprotonation and ylide formation, Wittig salts are well known to give a deep red colour.¹²⁶ In this case, there were brief signs of a red colouration upon addition of $n\text{-BuLi}$, however, this rapidly faded. It was concluded that this was caused by the presence of water and that the hygroscopic nature of the salt meant that even after drying under high vacuum it still retained water. The tetrafluoroborate salt **263** was therefore prepared and

was found to be far less hygroscopic. This was performed in a single step from 1,1-dimethoxyethane **260** in 94% yield using another procedure adapted from the literature.¹²⁵

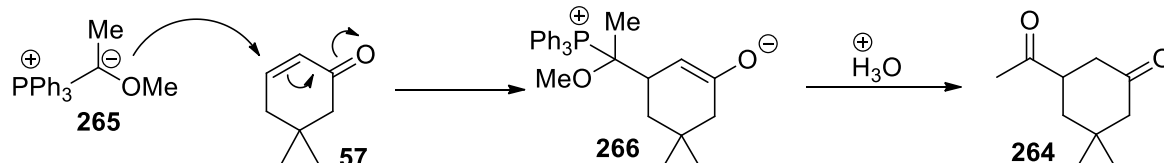


Scheme 58: Tetrafluoroborate salt preparation.

This salt retained its deep red colour upon deprotonation, however, was found to react in an unexpected fashion. The product **64**, obtained in a 45% isolated yield was actually a result of conjugate addition (minor levels of the product resulting from direct addition were also observed by GC-MS), (Scheme 59). The same selectivity was also observed when raising the temperature of the second step to -10°C , raising it further to room temperature resulted in decomposition. It is possible that intermediate **266** (Scheme 60) may be stabilised by intra- or intermolecular P-O interactions which may account for this behaviour.

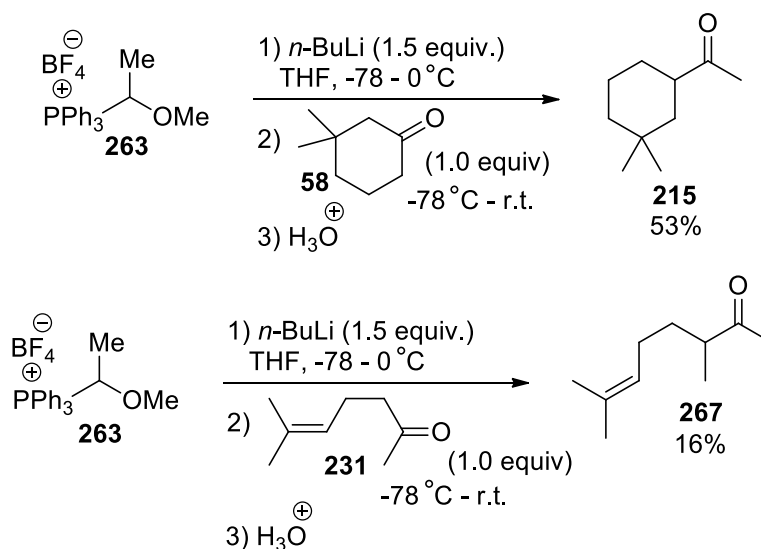


Scheme 59: Conjugate addition of (1-methoxyethyl)triphenylphosphonium tetrafluoroborate **263**.



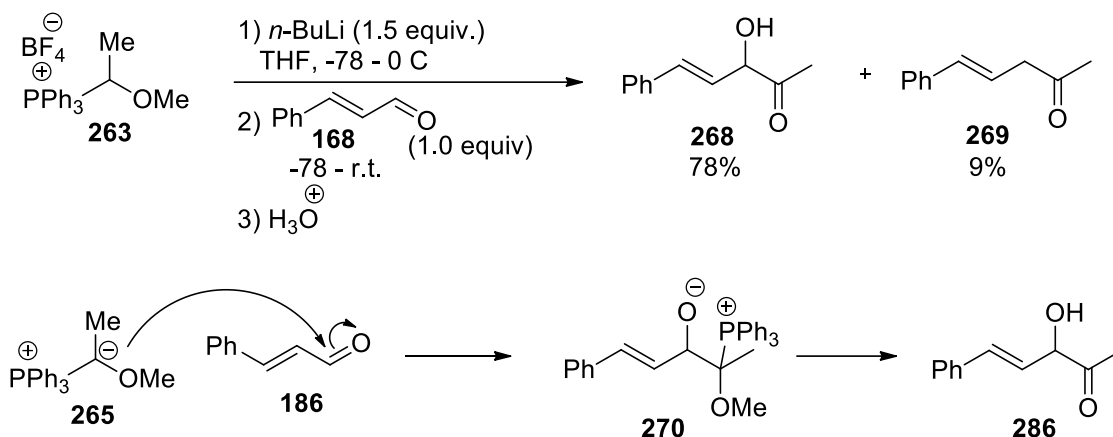
Scheme 60: Possible mechanism of formation of the conjugate addition product **264**.

In order to further explore this reactivity, the tetrafluoroborate salt **263** was also reacted with three other substrates **58**, **231** and **186** (Scheme 61 and 62). The saturated analogue, 3,3-dimethylcyclohexanone **58**, gave the product resulting from direct addition to the carbonyl group in 53% isolated yield. The reaction with the acyclic saturated ketone, 6-methyl-5-hepten-3-one **231**, also gave the product of direct addition although in low isolated yield. The Wittig reagent can therefore also react directly at carbonyl centres. To further explore its selectivity towards conjugate addition in the case of α,β -unsaturated aldehydes/ketones the reaction was attempted with the highly conjugated *trans*-cinnamaldehyde **186** (Scheme 62).



Scheme 61: Wittig reaction of tetrafluoroborate salt **263** with saturated ketones.

Interestingly, this yielded predominantly the unsaturated acyloin **268**. This presumably formed as a result of initial direct addition, giving intermediate **270**, which then underwent degradation to **268** under the reaction conditions (Scheme 62). The acyloin **268** was isolated in 78% yield and 9% of the standard Wittig product **269** was also isolated following column chromatography.



Scheme 62: Reaction of tetrafluoroborate salt **263** with *trans*-cinnamaldehyde.

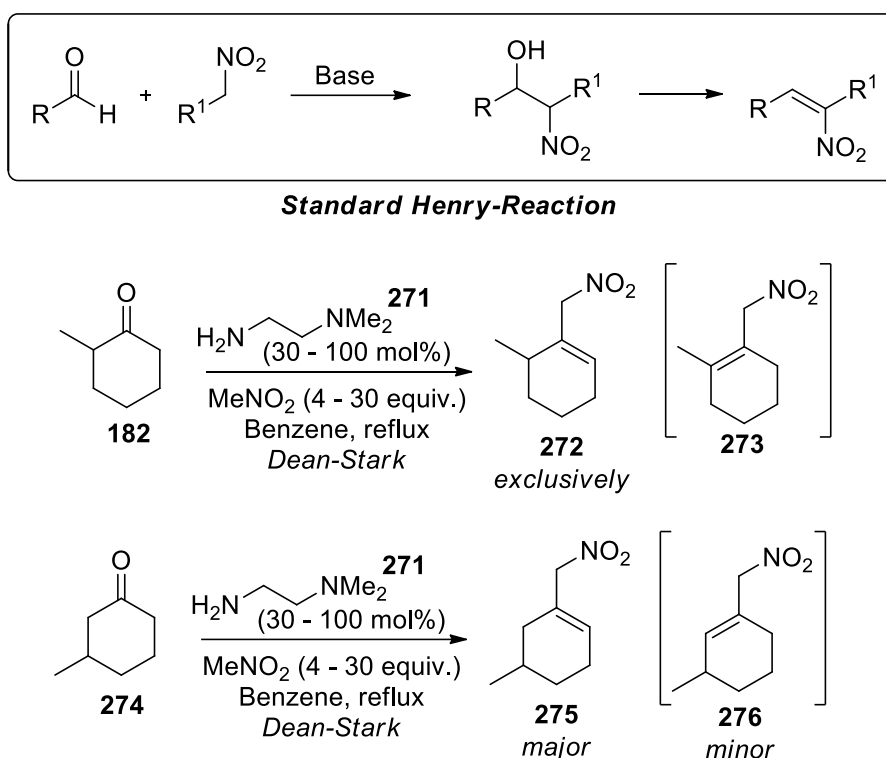
This particular Wittig reagent's propensity towards conjugate addition in the case of α,β -unsaturated carbonyl systems was previously unknown. Its unprecedented reactivity may be of interest to medicinal chemists, for example, however, this fell outside of the focused aims of this project and so it was not explored further.

In terms of atom economy, finding a Wittig route that was going to be economically competitive with IFFs current route is challenging. However, a Wittig route might allow access to a product with a high α -purity which could potentially be sold as a higher grade/quality specialty product. A Wittig route was not explored further as other routes were also investigated.

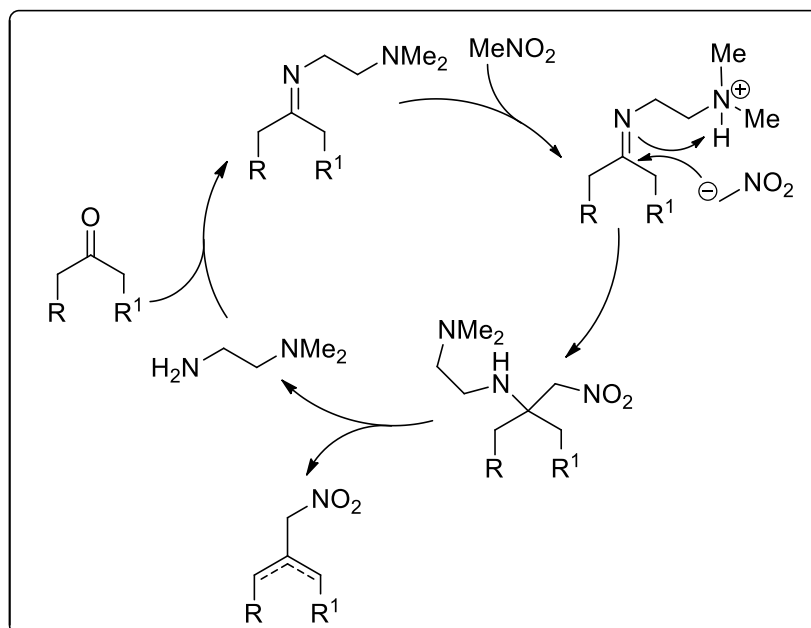
2.3.3. Alternative Synthetic Approaches Towards α -Dehydroherbac - An Irregular Nitro-Aldol Route

In 1982, a paper published by Barton detailed the use of imine catalysis for nitro-aldol reactions with nitromethane applied to the synthesis of corticosteroids.¹²⁷ This was later explored in more detail by Tamura *et al.*¹²⁸ where it was shown that *N,N*-dimethylethylenediamine **271** could be used as a catalyst for the formation of allylic nitro compounds from ketones and primary nitroalkanes. In a standard nitro-aldol or Henry reaction,¹²⁹ an intermediate alcohol is formed

which then undergoes elimination to give the double bond in the position directly adjacent to the nitro-group. In the methodology developed by Tamura, the products obtained were found to possess an allylic double bond. Of the many compounds prepared, two examples are given in Scheme 63. The reaction of 2-methylcyclohexanone **182** with nitromethane yielded exclusively the kinetic product **272**, this selectivity was also displayed for the reaction of 3-methylcyclohexanone **274** with nitromethane with the allylic nitro compound **275** being obtained as the major product (yields not given). The catalytic cycle shown in Scheme 64 was proposed.

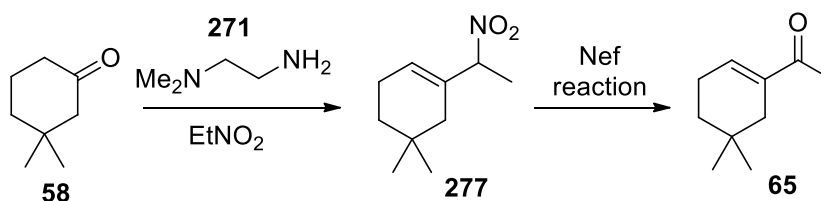


Scheme 63: Product double-bond selectivity in the *N,N*-dimethylethylenediamine catalysed nitro-aldol reaction vs. standard Henry reaction.



Scheme 64: Proposed catalytic cycle for the formation of allylic nitro compounds.

This methodology has more recently been used for the synthesis of a small collection of symmetrical cycloalkene allylic nitro compounds by Hayashi in a report concerning the development of molecular oxygen mediated Nef reactions.¹³⁰ However, it has received little or no attention with regards to the selective preparation of asymmetric cycloalkene allylic nitro compounds since its discovery in 1986. Considering the selectivity displayed for the synthesis of compound **272**, a similar preference in the position of double bond formation could also be expected with an analogous reaction of 3,3-dimethylcyclohexanone **58**. Such a reaction with nitroethane would give a product **277** that could be converted to dehydroherbac **65** in one step via a Nef reaction (Scheme 65). To our knowledge, this has never before been attempted.

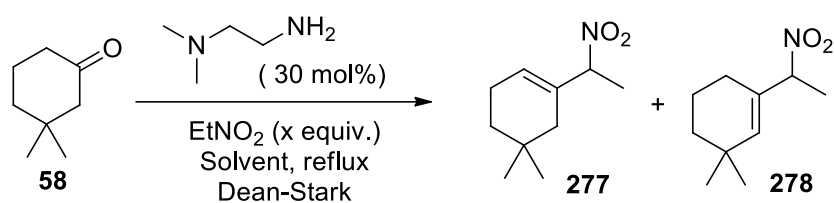


Scheme 65: Proposed route towards α -dehydroherbac **65** via a selective *N,N*-dimethylethylenediamine **271** catalysed nitro-aldol reaction and Nef oxidation.

2.3.3.1. Nitro-Aldol Process Development

As a preliminary study, commercially supplied 3,3-dimethylcyclohexanone **58** was treated with four equivalents of nitroethane and 0.3 equivalents of *N,N*-dimethylethylenediamine **271** in benzene (0.2 M) under Dean-Stark reflux to remove water. After 18 h, just 13% conversion was observed by GC-MS (calibration curves of a previously prepared and purified product sample set up with *n*-pentadecane as an internal standard), using ten equivalents of nitroethane resulted in improved kinetics, giving a 60% conversion after 72 h (Table 17, entry 2-4) with a 3.6:1 selectivity in favour of the desired α -product **277**.

Table 17: Initial solvent screening for the irregular nitro-aldol reaction of 3,3-dimethylcyclohexanone **58**.

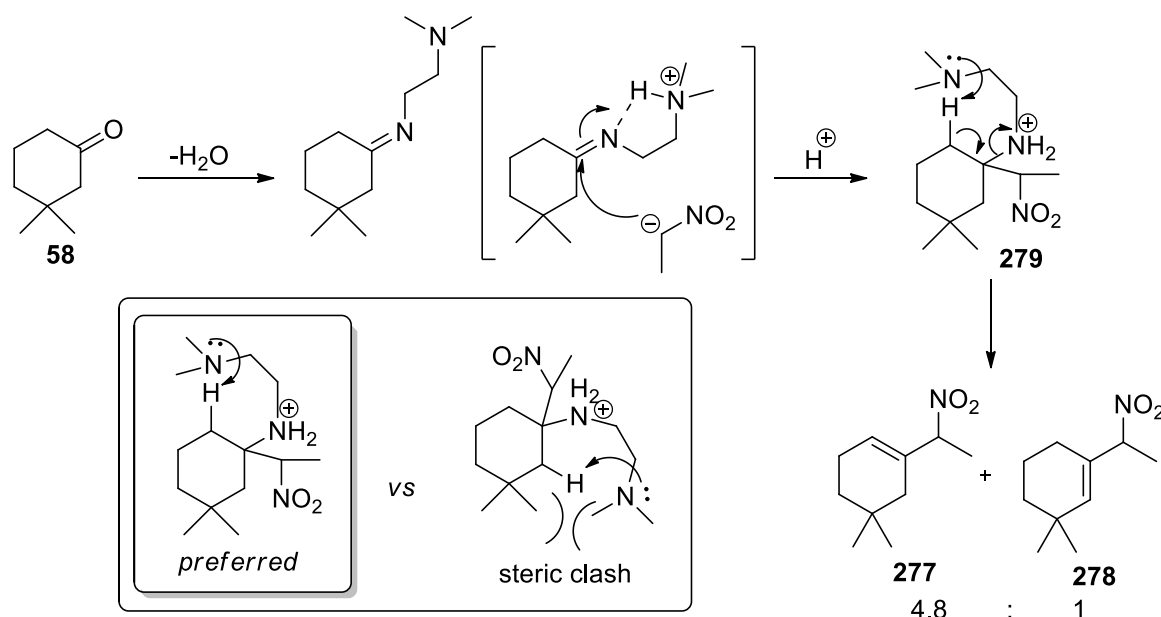


Entry	Solvent	Time	EtNO_2	α -Yield ^a	β -Yield ^a
1	Benzene	18 h	4 equiv.	10%	3%
2	Benzene	24 h	10 equiv.	28%	6%
3	Benzene	48 h	10 equiv.	34%	9%
4	Benzene	72 h	10 equiv.	47%	13%
5	Toluene	24 h	10 equiv.	9%	6%
6	Cyclohexane	24 h	10 equiv.	<1%	<1%
7	2-MeTHF	24 h	10 equiv.	1%	<1%
8	<i>i</i> PrOAc ^b	18 h	10 equiv.	53%	11%
9	EtOAc ^c	22 h	10 equiv.	53%	11%

Reactions conducted on 5 mmol scale at 0.2 M unless stated otherwise. ^a Yield estimated by GC-MS using *n*-pentadecane as an internal standard. ^b Loss of solvent through evaporation observed. ^c Reaction carried out at 1.0 M.

The use of benzene is now heavily regulated within industry, we therefore opted to evaluate alternate solvents which had a similar boiling point to benzene (b.p. 80 °C) to allow for efficient azeotropic removal of water without the loss of *N,N*-dimethylethylenediamine (b.p. 105 °C), (Table 17). Toluene gave an inferior yield as did cyclohexane and 2-methyl tetrahydrofuran (2-Me THF), Table 17, Entry 5-7). Isopropyl acetate, however, worked well giving 64% conversion with a 4.8:1 α -selectivity (Table 17, Entry 8). Some loss of solvent through evaporation occurred due to a leak in the reactor in this experiment meaning that the concentration was higher than with other solvents, this was later found to be advantageous. This result was subsequently reproduced with ethyl acetate solvent by carrying out the reaction at 1.0 M preventing any solvent evaporation (Table 17, Entry 9).

The observed regioselectivity is consistent with Tamura's results and can be explained by considering the sterics involved in the deprotonation of the diamine adduct **279** (Scheme 66). The presence of a *gem*-dimethyl group on the ring and the *N*-dimethyl functionality gives rise to a preference towards deprotonation at the ' α ' β -carbon (less steric interactions) giving the α -dehydroherbac precursor **277** as the major product.



Scheme 66: Mechanistic rationalisation of observed selectivity.

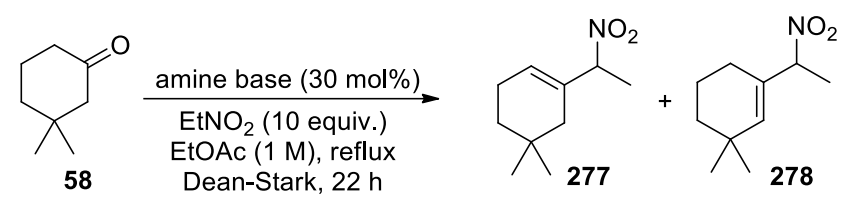
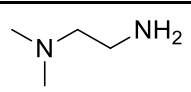
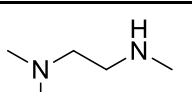
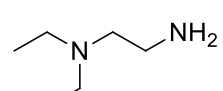
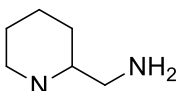
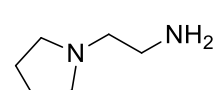
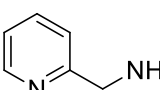
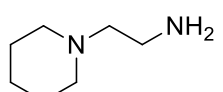
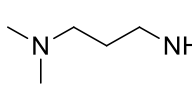
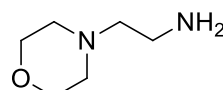
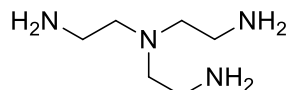
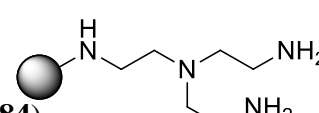
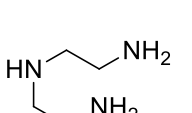
Other reactor setups were considered briefly and it was shown that molecular sieves were also effective at removing water from the reaction (69% conversion after 22h). Carrying out the reaction in a sealed tube under various conditions revealed that water removal was necessary and that carrying the process over to flow would be difficult. The Dean-Stark setup was chosen going forward along with ethyl acetate due to it being cheap, green and possessing a slightly lower boiling point than isopropyl acetate.

Concentration was found to be key in determining reaction times, however, upon increasing the concentration, the internal reactor temperature also increased due to the increased ratio of nitroethane to EtOAc (nitroethane b.p. 114 °C). This became a problem when reaching internal temperatures that were high enough to cause significant evaporation of the amine base as it would become trapped in the aqueous layer of the Dean-Stark trap. Carrying out the reaction neat was not practical due to the fact that nitroethane is denser than water, making removal of water by Dean-Stark impractical. A series of bases with higher boiling points were therefore considered and employed for reactions at 1.0 M in EtOAc (concentration required for full starting material consumption in less than 1 day) with 10 equivalents of nitroethane and 30 mol% of the base (Table 18).

The problem of base evaporation was eliminated in the case of all other bases tested. The best results were obtained using 1-(2-aminoethyl)pyrrolidine **281** - 81% yield obtained after 22 hours with a selectivity of 8.2:1. Both the piperidine **282** and diethyl **280** derivatives also proved effective, with compound **280** giving comparable yields, but with an inferior product ratio (5.3:1). The polymer-supported trisamine **284** was unsuccessful and other trisamine derivatives **289** and **290** also gave poor yields. The secondary amine equivalent **285** was used to test whether the reaction could also proceed through an iminium-type mechanism, this resulted in a very poor yield validating the imine-based mechanism proposed in Scheme 66. The pyridine derivative **287** was also unsuccessful, suggesting that the lone pair of the tertiary

nitrogen of the base plays a key role in the reaction (pyridine conjugate acid $pK_a \sim 5$ vs. triethylamine conjugate acid $pK_a \sim 11$ in H_2O). Interestingly, the chain extended derivative **288** gave only a 5% yield of the products suggesting that the tertiary nitrogen needed to be specifically positioned in order to deprotonate the ' α ' β -carbon. These findings also help to validate the proposed mechanism. The use of additives such as 1-benzyl-3-phenylurea and *p*-toluenesulfonic acid appeared to have no effect on either the yield or rate of the reaction.

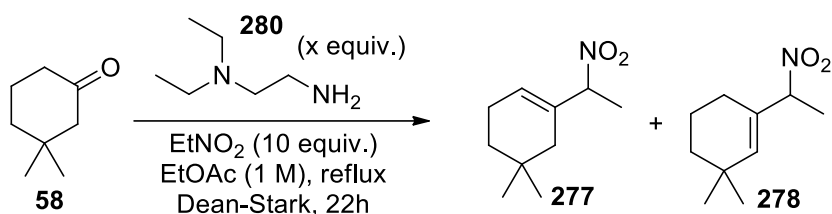
Table 18: Base screening for the irregular nitro-aldol reaction of 3,3-dimethylcyclohexanone.

							
Entry	Base	b.p./°C	Yield ^a (α : β)	Entry	Base	b.p./°C	Yield ^a (α : β)
1 (271)		105	64% (4.9)	7 (285)		117	6% (3.1)
2 (280)		146	80% (5.3)	8 (286)		190	42% (3.4)
3 (281)		160	81% (8.2)	9 (287)		200	0
4 (282)		186	70% (4.8)	10 (288)		133	5% (4.1)
5 (283)		224	32% (3.6)	11 (289)		240	30% (4.2)
6 (284)			<1%	12 (290)		200	29% (2.5)

Reactions carried out on 50 mmol scale at 1.0 M. ^a Yield estimated by GC-MS using *n*-pentadecane as an internal standard.

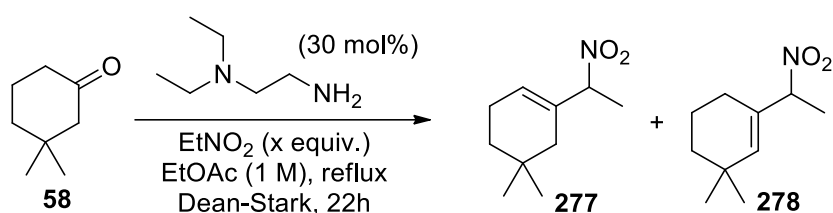
Despite the fact that the optimum result was obtained with the pyrrolidine derivative **281**, the diethyl derivative **280** was selected moving forward due to its more attractive price (£0.18/g *diethyl 280* vs £0.58/g *dimethyl 271* vs £5.72/g *pyrrolidine 281*, Sigma-Aldrich prices for 100 g or less). Varying the stoichiometry of the base and nitroethane revealed that lowering the amounts of either in the reaction is feasible to some extent but that longer reaction times become necessary by doing so (Table 19 and 20).

Table 19: Variation of base stoichiometry.



Entry	base equiv.	Yield ^a	$\alpha:\beta$ ratio
1	5 mol%	37%	2.0
2	15 mol%	67%	4.4
3	30 mol%	80%	5.3
4	60 mol%	66%	4.9
5	100 mol%	41%	3.0

Reactions carried out on 50 mmol scale at 1.0 M. ^a Yield estimated by GC-MS using *n*-pentadecane as an internal standard.

Table 20: Variation of nitroethane stoichiometry.

Entry	EtNO ₂ equiv.	Yield ^a	α : β ratio
1	2.5	33%	5.6
2	5	62%	5.7
3	10	80%	5.3

Reactions carried out on 50 mmol scale at 1.0 M. ^a Yield estimated by GC-MS using *n*-pentadecane as an internal standard.

By monitoring the reaction concerning the diethyl base **280** over prolonged periods it was revealed that the α : β ratio deteriorates over time. A mixture containing 14:1, **277**:**278** (obtained by column chromatography of a 5.4:1 **277**:**278** mixture) was subjected to the reaction conditions at greater than 100 °C in a sealed vial and the content of the mixture was monitored over the period of 6 days, this was conducted on a 1 mmol scale. Using 1,3,5-trimethoxybenzene as an internal standard, the quantity of each of the isomers was monitored using sampling ¹H-NMR analysis. This revealed decomposition of the α -isomer **277** (Figure 26) and that the β -isomer **278** was relatively stable. The fact that the content of the β -isomer **278** never increased upon the initial 7% rules out interconversion as a possible explanation for the observed α : β ratio deterioration. This experiment was repeated at 100 °C on a 5.4:1, **277**:**278** mixture (Figure 27) and the same behaviour was exhibited but with a slower rate of decomposition. The above studies would suggest that the observed deterioration of the α : β ratio is therefore simply due to faster α -isomer **277** decomposition. It is possible that the decomposition pathway follows initial reprotonation at the allylic carbon (Scheme 67). If this is indeed the case, it offers a possible explanation for why decomposition of the α -isomer **277** is more rapid as reprotonation at this position would be more facile due to steric arguments.

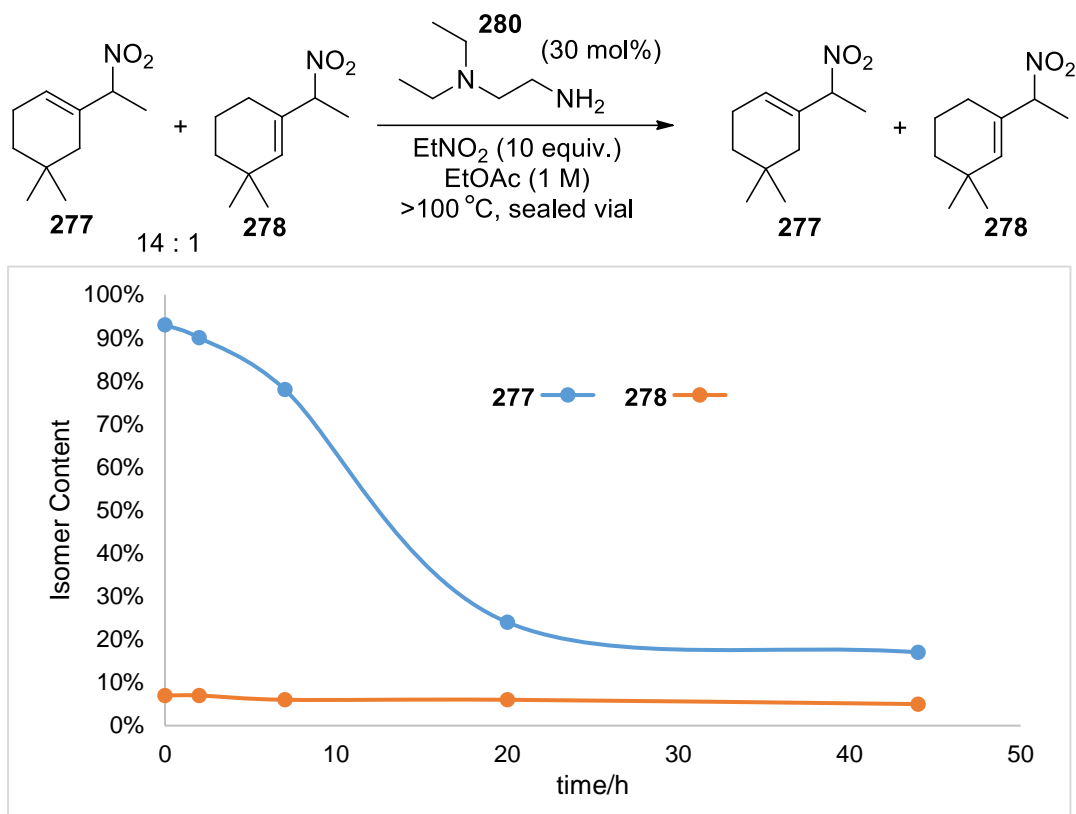


Figure 26: Content of a 14:1 $\alpha:\beta$ isomer mixture vs. time at >100 °C under the reaction conditions.

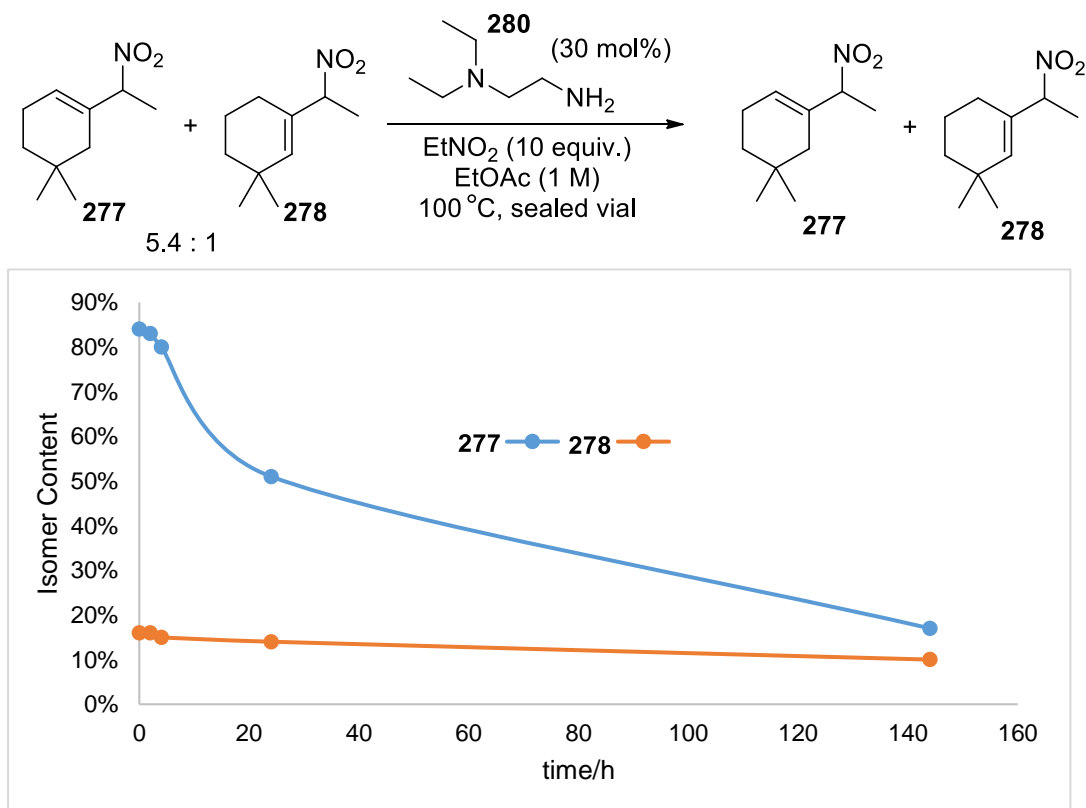
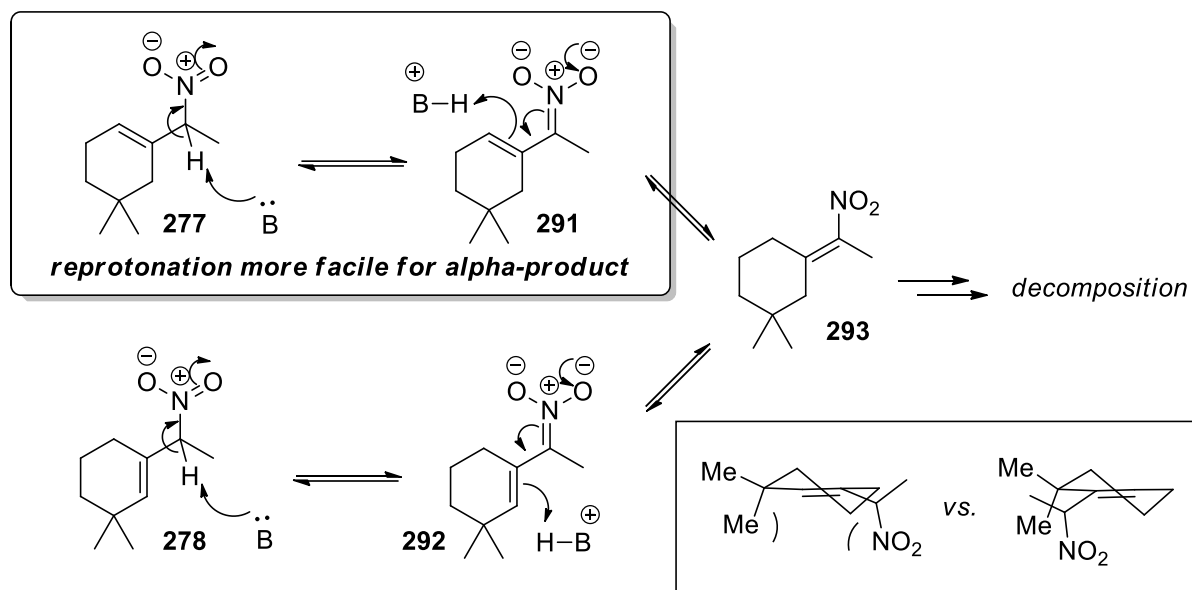
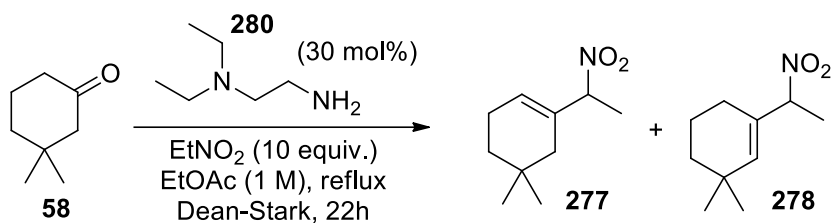


Figure 27: Content of a 5.4:1 $\alpha:\beta$ isomer mixture vs. time at 100 °C under the reaction conditions.



Scheme 67: Reprotonation as an explanation for more rapid decomposition of α -product.

With the decomposition in mind, we elected to constrain the reaction within a 24 h timeframe. Longer reaction times would result in an inferior $\alpha:\beta$ ratio and shorter reaction times would give a lower yield. The process was scaled up (to 0.5 mol scale) using the conditions earlier identified (30 mol% diethyl base, 10 equiv. EtNO_2 , 1 M in EtOAc) and the product was isolated by distillation (Table 21). It was found that an acid wash prior to distillation was vital in order to avoid co-distillation of an unidentified side product. Evaporation of the nitroethane before carrying out the acid wash was also favourable as nitroethane is more dense than water and its presence leads to poor phase separation. Significant residue was left behind (~ 17 g at 0.5 mol scale) following distillation, this was due to decomposition products. Decomposition of the amine base was also observed as none could be recovered, further strengthening the case for using the cheaper amine **280**. It was speculated that adding the base portion-wise to the reaction would result in superior yields and this was indeed found to be the case. Under the final optimised protocol (Table 21, Entry 3) the product was obtained in 78% isolated yield (5.4:1 selectivity) after distillation.

Table 21: Scale-up reactions.

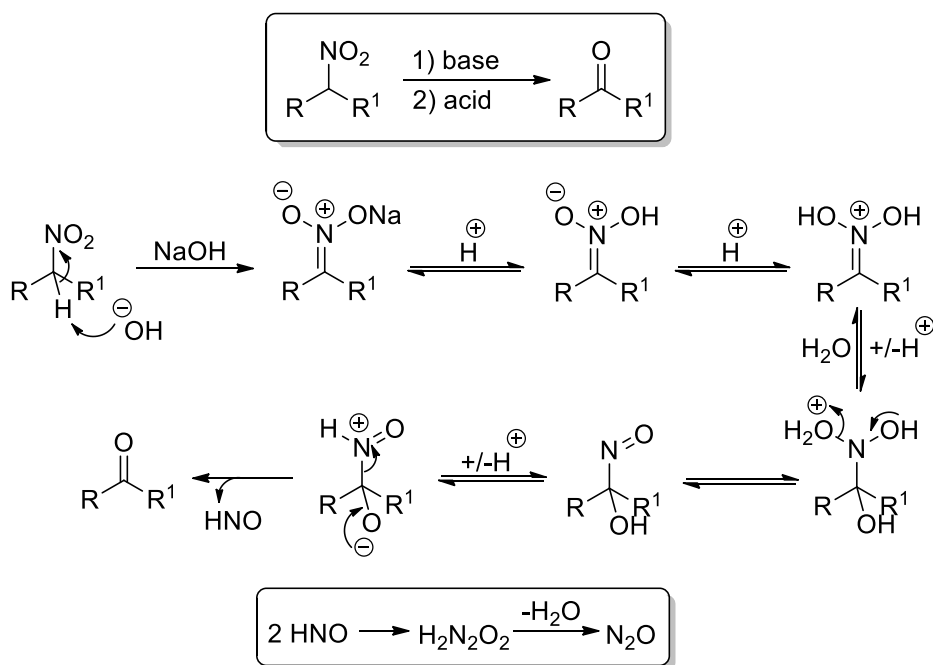
Entry	Work-up conditions	Comments	Isolated yield	$\alpha:\beta$ ratio
1	Amine residues extracted using a 1 M aq. HCl wash prior to distillation	EtOAc (quantitative), starting material (9%) and EtNO ₂ (96%) all recovered by distillation	73%	5.7:1
2	Crude product distilled directly	Co-evaporation of side-product during distillation of product	76%	5.2:1
3 ^a	EtNO ₂ evaporated, then amine residues extracted using a 1 M aq. HCl wash prior to distillation	Base added portion-wise (3 portions (0 h, 3 h, 6 h))	78%	5.4:1

Reactions performed on 0.50 mol scale unless stated otherwise at 1.0 M. ^a Performed on 0.30 mol scale.

2.3.3.2. Nef Reaction Development

The Nef reaction¹³¹ (Scheme 68) involves the formation of a carbonyl compound from a primary or secondary nitroalkane. Initial treatment with a base such as sodium hydroxide leads to the formation of a nitronate salt, under classical conditions, this is treated with aqueous acid to furnish the corresponding ketone, with nitrous oxide being extruded as a by-product. This nitro to carbonyl transformation has become a valuable tool to synthetic chemists due to the potential for “umpolung” reactivity when coupled with a Henry reaction, acting as an acyl anion equivalent. The formation of the nitronate salt is usually straightforward and occurs in high yield, the key step in determining the overall yield of the reaction is the acidification step.

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Initially, a range of such non-classical methods for conducting the Nef reaction were investigated as a scoping exercise (Table 22) using conditions from the literature.^{130, 135-138} The best results, however, were achieved under the classical conditions represented in Table 22, entry 4/7 (treatment with aqueous hydrochloric/sulfuric acid after nitronate salt formation).

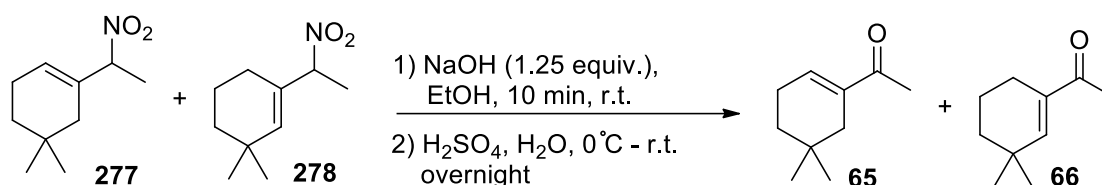
Table 22: Initial scoping of Nef reaction methods.

Entry	Conditions	α -yield ^a	β -yield ^a
1	1) NaOH, EtOH 2) Riboflavin, H ₂ O	<1%	<1%
2	Riboflavin, MeOH/H ₂ O*	0%	0%
3	HCl, MeOH*	0%	0%
4	1) NaOH, EtOH 2) HCl, H ₂ O	36%	7%
5	HCl/AcOH (2:1), neat*	0%	0%
6	H ₂ O ₂ , K ₂ CO ₃ , MeOH*	16%	5%
7	1) NaOH, EtOH 2) H ₂ SO ₄ , H ₂ O	38%	6%
8	KO ^t Bu, O ₂ , MeCN*	21%	5%
9	DBU, O ₂ , MeCN*	27%	6%
10	1) NaOH, EtOH 2) O ₂	2%	<1%

Reactions performed on 3 mmol scale, starting material 85:15, α : β . *No separate nitronate formation step.

^a Conversion determined by ¹H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

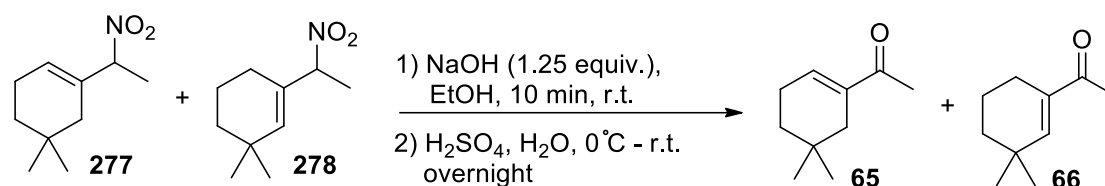
Sulfuric acid gave the best result and so was used going forward, the temperature was fixed at room temperature for the first step and 0 °C for the second step. The amount of ethanol used was fixed at 1.7 mL/mmol starting material (SM) as this was the highest concentration that could be used without precipitation of the nitronate salt. The amount of H₂O and H₂SO₄ used during the second step were used as the variables for a small DoE. The parameter window initially used for a full factorial design was relatively large (1 – 5 mL H₂O/mmol of SM and 0.5 – 3 equivalents of sulfuric acid). From the first study, the optimum result obtained (50% α -yield, 8% β -yield) was at 3 equiv. of H₂SO₄ and 1 mL H₂O/mmol of SM (Table 23).

Table 23: DoE optimisation of H₂SO₄ vs. H₂O equivalents, first round.

Entry	Pattern	H ₂ SO ₄ (equiv.)	H ₂ O (mL/mmol of SM)	α -yield ^a	β -yield ^a
1	+ -	3	1	50%	8%
2	++	3	5	39%	6%
3	- +	0.5	5	4%	1%
4	--	0.5	1	5%	1%
5	0 0	1.75	3	36%	6%
6	0 0	1.75	3	37%	6%

Reactions performed on 3 mmol scale, starting material 87:13, α : β . +, - and 0 represent the upper extremity, mid-point value and lower extremity respectively.^a Conversion determined by ¹H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

A second optimisation (Table 24) was then performed with a window centred on this optimum point, investigating the reaction space associated with the highest yield in Table 23. However, none of the yields obtained were as high as that of the optimum from the first DoE exercise (Table 23, entry 1). Further investigation revealed that using 2 equiv. H₂SO₄ along with 0.5 mL H₂O/mmol of SM give an equivalent yield to the previously established 3 equiv. H₂SO₄, 1 mL H₂O/mmol of SM conditions (Table 23, entry 1). These two sets of conditions presumably represent highly favorable points in terms of pH/water content for the formation of the ketones **65** and **66** from the nitronate salts **277** and **278**. These were therefore taken moving forward.

Table 24: DoE optimisation of H₂SO₄ vs. H₂O equivalents, second round.

Entry	Pattern	H ₂ SO ₄ (equiv.)	H ₂ O (mL/mmol of SM)	α -yield ^a	β -yield ^a
1	+ -	6	0.3	31%	6%
2	++	6	3	39%	8%
3	- +	1.75	3	37%	6%
4	--	1.75	0.3	39%	8%
5	0 0	3.88	1.65	44%	8%
6	0 0	3.88	1.65	42%	8%

Reactions performed on 3 mmol scale, starting material 87:13, α : β . +, - and 0 represent the upper extremity, mid-point value and lower extremity respectively. ^a Conversion determined by ¹H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

Finally, with the above conditions in hand, the reactions detailed in Table 25 were run in order to obtain representative isolated yield values. The best result was obtained using 2 equiv. H₂SO₄, 0.5 mL H₂O/mmol SM – the product was isolated using distillation and obtained in 65% yield. In all cases, significant residues remained following distillation (due to product decomposition during distillation). Retention of the α : β (**65**:**66**) ratio was also observed in all cases.

Table 25: Scale-up of established reaction conditions.

Reaction scheme: 277 + 278 $\xrightarrow[2) \text{ conditions}]{1) \text{ NaOH (1.25 equiv.)}}$ 65 + 66

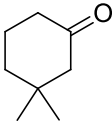
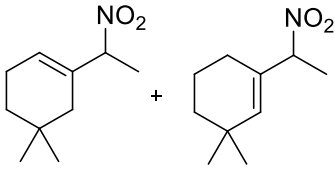
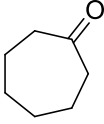
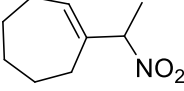
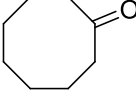
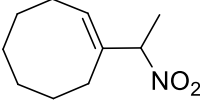
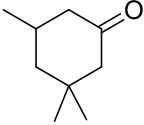
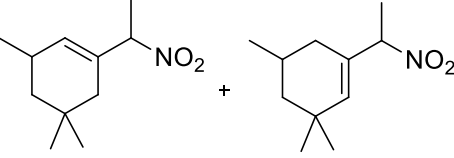
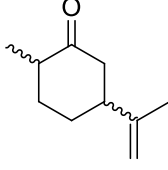
Entry	Scale	Conditions	Isolated yield
1	33 mmol	H ₂ SO ₄ (3 equiv.), H ₂ O (1 mL/mmol SM), 0 °C – r.t., 3 h.	62% after column
2	82 mmol	H ₂ SO ₄ (3 equiv.), H ₂ O (1 mL/mmol SM), 0 °C – r.t., 3 h.	63% after distillation
3	82 mmol	H ₂ SO ₄ (2 equiv.), H ₂ O (0.5 mL/mmol SM), 0 °C – r.t., 3 h.	65% after distillation

2.3.3.3. Application of Developed Methodology to Other Substrates

The final conditions for the two-step synthesis of α -dehydroherbac were next applied to a range of other cyclic substrates (Table 26 and 27). The nitroaldol reaction was first investigated with nitroethane (Table 26, Entry 1 – 6). Increasing the ring size generally led to a drop in yields with cycloheptanone **294** yielding the nitro olefin **295** in 61% isolated yield and cyclooctanone **296** yielding the product **297** in 39% (Table 26, Entry 2 and 3). The reaction of 3,5,5-trimethylcyclohexanone **298** displayed the same preference towards the product requiring deprotonation at the less sterically hindered position (Table 26, Entry 4), however, with a lower selectivity (1.9:1, **299**:**300**). The reaction of nitroethane with dihydrocarvone **301**, a substrate possessing α -methyl functionality, gave only traces of the product (GC-MS) after 48 h suggesting that α -substituted ketone systems are not compatible with nitroethane (Table 26, Entry 5). The reaction with menthone **302**, possessing α -isopropyl functionality led to no reaction with nitroethane, further reinforcing this hypothesis (Table 26, Entry 6). Upon reaction with nitromethane, however, menthone **302** delivered the nitro olefins **306** and **307** in 89%

isolated yield (3.3:1, **306:307**), again with selectivity directed towards the product requiring deprotonation at the less sterically hindered position **306** (Table 26, entry 9). Treatment of dihydrocarvone **301** with nitromethane gave only traces of the products (GC-MS), (Table 26, Entry 10).

Table 26: Nitro olefins prepared using the developed methodology.

$ \begin{array}{c} \text{R}^1\text{CH}_2\text{C(=O)CH}_2\text{R}^2 \\ \xrightarrow[\text{EtOAc (1 M), reflux; Dean-Stark, 22 h}]{\text{Et/Me/PrNO}_2 \text{ (10 equiv.)}, \text{EtN(CH}_2\text{CH}_3)_2 \text{ (30 mol\%)}} \\ \text{R}^1\text{CH=CHCH(Me/H)NO}_2 + \text{R}^1\text{CH}_2\text{CH=CHCH(Me/H)NO}_2 \end{array} $				
Entry	Ketone	Nitroalkane	Product	Isolated Yield (%)
1 ^a (58)		EtNO ₂		78% (277+278) (5.4:1)
2 (294)		EtNO ₂		61% (295)
3 (296)		EtNO ₂		39% (297)
4 (298)		EtNO ₂		25% (299+300) (1.9:1)
5 (301)		EtNO ₂	traces of product observed by GC-MS	-

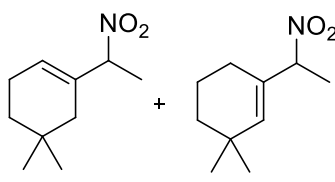
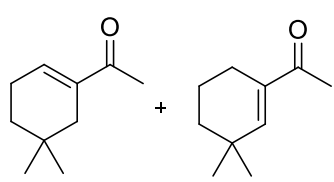
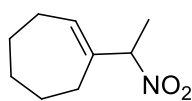
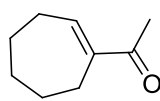
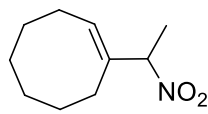
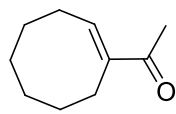
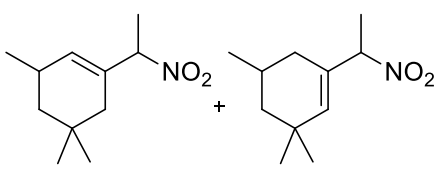
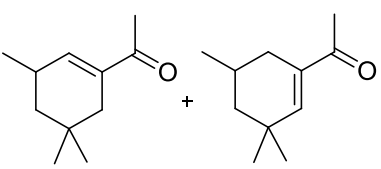
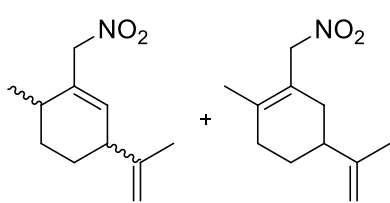
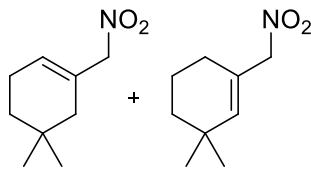
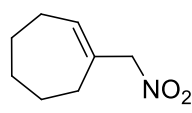
6 (302)		EtNO ₂	no reaction	-
7 (58)		MeNO ₂		94% (303+304) (3.0:1)
8 (294)		MeNO ₂		75% (305)
9 (301)		MeNO ₂		89% (306+307) (3.3:1)
10 (302)		MeNO ₂	traces of product observed by GC-MS	-
11 (58)		<i>n</i> -PrNO ₂	no reaction	-
12 (294)		<i>n</i> -PrNO ₂	no reaction	-
13 (294)		<i>i</i> PrNO ₂	no reaction	-

Reactions conducted on 50 mmol scale unless stated otherwise. ^a Reaction carried out on 0.50 mol scale.

The reaction of nitromethane with 3,3-dimethylcyclohexanone **58** and cycloheptanone **294** also progressed smoothly delivering the nitroolefins **303/304** in 94% (3.0:1) and **305** in 75% isolated yield (Table 26, Entry 7-8). Upon reaction of 3,3-dimethylcyclohexanone **58** and

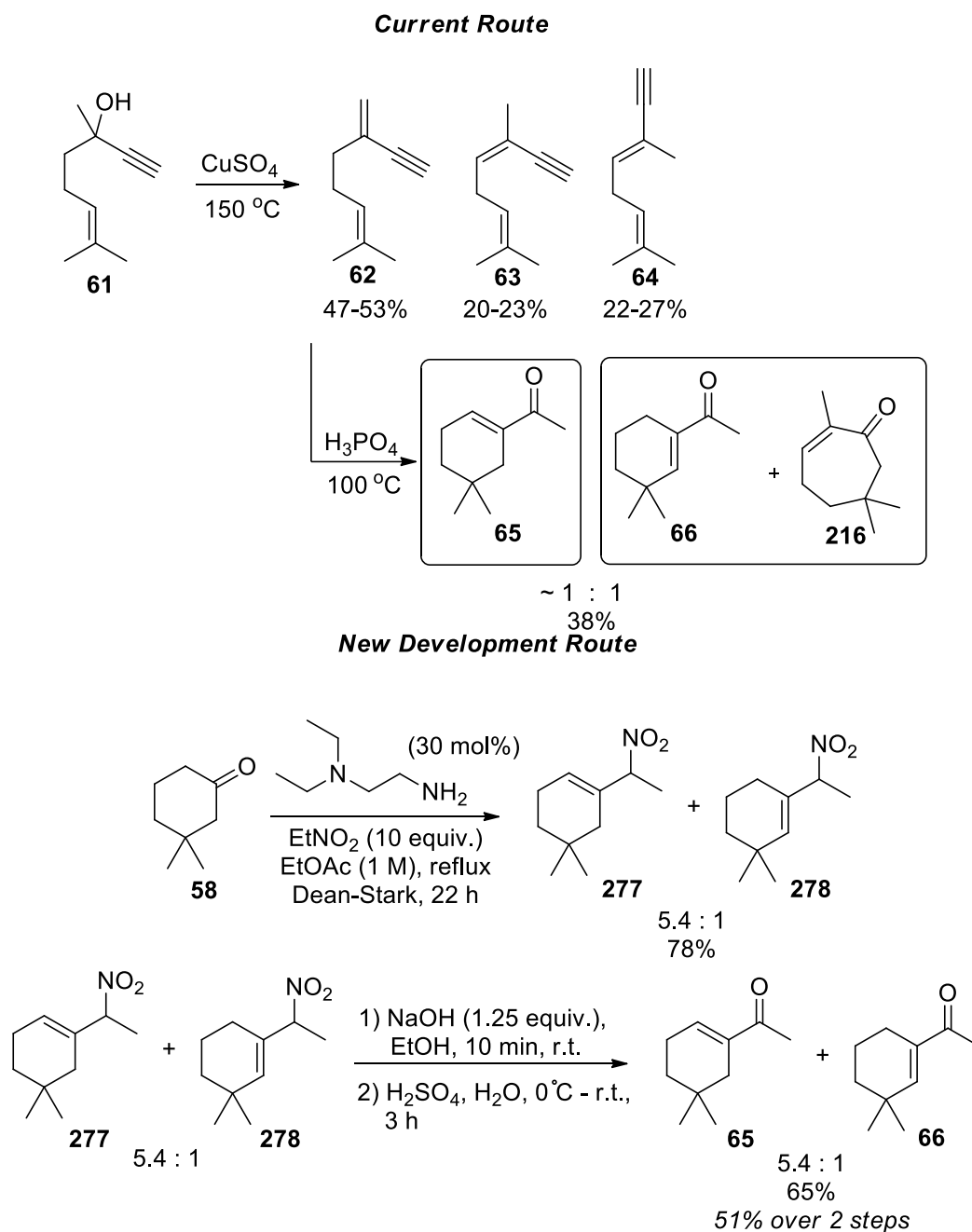
cycloheptanone **294** with 1-nitropropane (Table 26, Entry 11-12), no product formation was observed suggesting that the reaction is limited to nitroethane and nitromethane. The same-behavior was exhibited for the reaction with 2-nitropropane (Table 26, Entry 13). It is likely that the increased steric demand from these nitro species mean that a formation of an intermediate similar to **279** (Scheme 66) is not possible. Unoptimised Nef reactions of the obtained secondary nitro olefins obtained gave the corresponding ketones in moderate yields with retention of the isomer ratios (Table 27). In the case of primary nitro olefins **303** - **307**, starting material was mostly recovered. The conversion of primary nitroolefins to aldehydes is known,¹¹² however, alternative conditions are clearly required for this. Achieving this fell beyond the scope of this project so alternative conditions were not investigated.

Table 27: Nef reaction of nitro olefins.

$ \begin{array}{c} \text{Me/H} \\ \\ \text{R}^1\text{---}\text{C}=\text{C}\text{---}\text{CH}\text{---}\text{NO}_2 \\ \\ \text{R}^2 \end{array} \xrightarrow[\begin{array}{c} \text{2) H}_2\text{SO}_4 \text{ (2 equiv.)}, \\ \text{H}_2\text{O (0.5 mL/mmol SM)}, \\ 0^\circ\text{C} - \text{r.t.}, \text{ overnight} \end{array}]{ \begin{array}{c} \text{1) NaOH (1.25 equiv.)}, \\ \text{EtOH, 10 min, r.t.} \end{array} } \begin{array}{c} \text{Me/H} \\ \\ \text{R}^1\text{---}\text{C}=\text{C}\text{---}\text{C}=\text{O} \\ \\ \text{R}^2 \end{array} $			
Entry	Nitro olefin	Product	Isolated Yield (%)
1 (277+278)			65% (65+66) (5.4:1)
2 (295)			42% (308)
3 (297)			47% (309)
4 (299+300)			54% (310+311) (1.9:1)
5 (306+307)		traces of product observed by GC-MS	-
6 (306+307)		traces of product observed by GC-MS	-
7 (305)		no reaction	-

Reactions conducted on 6 – 82 mmol scale.

2.3.4. Summary and Conclusion



Scheme 69: Current IFF route *vs.* new development route.

The dehydration-rearrangement of dehydrolinalool was studied and a mechanism was proposed (Scheme 53). Two new routes towards α -dehydroherbac were investigated. The first was unsuccessful but revealed interesting reactivity of Wittig salt **263**. The second route starts from cheap, easily accessible starting materials^{125, 141} and was successful, giving a product with a far

superior $\alpha:\beta$ (**65:66**) ratio (5.4:1 vs. 1:1) than is currently obtained by IFF's industrial route in a higher yield (51% over two steps vs. 38%).

3. Conclusion and Future Perspectives

In summary, three primary projects were undertaken, each relevant to the synthesis of an industrially important fragrance compound. Multiple new reactions/processes have been developed as a result of this and key features of two of IFF's current manufacturing processes have been established. The work described here covers only three of many hundreds¹⁴⁰ of synthetic F&F materials currently produced in the industry. Of the three investigated, it was possible to improve upon currently used industry processes using new chemistry in two cases. For one of these, a feasible flow process was also established. Considering the conservative nature of the F&F industry and the fact that many synthetic protocols currently used are based on old patents, there are undoubtedly many more synthetic F&F ingredients for which improved synthetic protocols could be realised both in batch and flow. However, much more work is needed to fully assess the crossover between the areas of flow chemistry and the F&F industry. Future work in this area should focus specifically on reactions for which there are obvious advantages to be gained by adopting a flow approach, for example, thermal Diels-Alder reactions or reactions involving hazardous materials/products. Further work is also needed to evaluate the logistical aspects of implementing flow processes alongside common techniques in the industry such as distillation. This thesis clearly demonstrates a significant scope for improvement upon current F&F industry processes through the utilisation of alternative synthetic approaches. The industry is now showing a keen interest in topics such as biocatalysis in efforts to achieve this and these areas of research will become increasingly important looking forward.

4. Experimental

4.1. Materials and Methods

Unless otherwise stated, all solvents were purchased from Fisher Scientific and used without further purification. Dry solvents were obtained by filtration through a column of Al₂O₃. Substrates, their precursors and reagents were purchased from either Alfa Aesar, Sigma Aldrich, Fluorochem, TCI, Carbosynth or Acros Organics or supplied by IFF and used as received.

¹H-NMR spectra were recorded on either Bruker Avance-400 or Varian VNMRs-700 instruments and are reported relative to residual solvent: CHCl₃ (δ 7.26 ppm), DMSO (δ 2.50 ppm), MeOH (δ 3.31 ppm), H₂O (δ 4.79 ppm). ¹³C-NMR spectra were recorded on the same instruments and are reported relative to CDCl₃ (δ 77.16 ppm). Data for ¹H-NMR are reported as follows: chemical shift (δ/ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, s, br = broad singlet, app. = apparent. Data for ¹³C-NMR are reported in terms of chemical shift (δ_C/ ppm). DEPT-135, COSY, HSQC, HMBC, PSYCHE and NOESY experiments were used in structural assignments.

IR spectra were obtained using a Perkin Elmer Spectrum Two UATR Two FT-IR Spectrometer (neat, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of tallest signal), medium (m, 21-70% of tallest signal) or strong (s, >71% of tallest signal).

Low and high resolution mass spectrometry were performed using the indicated techniques.

Low resolution gas chromatography mass spectrometry (GC-MS) was performed on a

Shimadzu QP2010-Ultra equipped with an Rxi-5Sil MS column (0.15 μ m x 10m x 0.15 mm) in EI mode. Low and high resolution atmospheric solids analysis probe mass spectrometry (ASAP-MS) was performed using a Waters LCT Premier XE. Low resolution liquid chromatography mass spectrometry (LC-MS) was performed using a Waters TQD mass spectrometer and an Acquity UPLC BEH C18 1.7 μ m column (2.1mm x 50mm) in ESI mode. ESI-HRMS was performed using a Waters QtoF Premier mass spectrometer. For accurate mass measurements the deviation from the calculated formula is reported in ppm. Melting points were recorded on an Optimelt automated melting point system with a heating rate of 1 °C/min and are uncorrected.

Reactions were conducted in flow using the following equipment: Vapourtec Manual Control RS-100 (isocratic), Vapourtec E-series easy-Medchem (peristaltic), Knauer compact HPLC pumps, ThalesNano H-Cube reactor and an AM Technology CoFlore ACR along with standard PTFE tubing and reactor coils. Microwave reactions were performed using a Biotage Initiator+ microwave reactor.

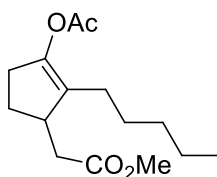
SiO₂ column chromatography was performed using Sigma Aldrich silica gel (grade 9385, pore size 60A) and standard manual column apparatus or GraceResolvTM pre-packed columns with a Biotage Isolera Four automated system. For TLC, Sigma Aldrich glass-backed plates were used and visualisation was performed using UV-irradiation or a KMnO₄ stain. Organic solutions were concentrated under reduced pressure using a Buchi rotary evaporator and high vacuum was achieved using an Edwards RV5 pump and Schlenk line. Kugelrohr distillation was performed using a Buchi Glass Oven B-3585 and vacuum distillation was performed using a Buchi V-700 vacuum pump equipped with a V-850 vacuum controller, or an Edwards RV E2M2 pump for lower pressures, attached to a standard distillation pig setup.

4.2. Hedione

General Procedure for Acetylation of Ketones/Aldehydes

For a typical 10.0 mmol scale reaction, the starting material was dissolved in isopropenyl acetate (2.2 mL, 2 equiv.) and *p*-TSA (0.20 g, 10 mol%) was added. The resulting mixture was stirred at 90 °C until full conversion was achieved (TLC). Saturated aqueous NaHCO₃ (15 mL) and Et₂O (20 mL) were added and the products were extracted using further Et₂O (2 x 20 mL). After drying over Na₂SO₄ and concentration *in vacuo*, the crude products were purified using SiO₂ column chromatography (hexane/EtOAc) where necessary.

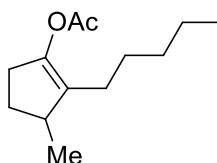
Methyl 2-(3-acetoxy-2-pentylcyclopent-2-en-1-yl)acetate¹⁴¹ **24**



Chemical Formula: C₁₅H₂₄O₄
Molecular Weight: 268.35

Pale brown liquid (5 mmol scale, 1.31 g, 98%), *R*_f (9:1, hexane:EtOAc) 0.3. ¹H NMR (400 MHz, CDCl₃) δ 3.70 (s, 3H), 3.07 (m, 1H), 2.56 (dd, *J* = 4.4, 14.8 Hz, 1H), 2.48 (m, 2H), 2.14 (s, 3H), 2.24-2.07 (m, 3H), 1.80 (m, 1H), 1.63 (m, 1H), 1.42 (m, 1H), 1.27 (m, 5H), 0.90 (t, *J* = 7.9 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 173.3, 168.6, 145.2, 128.3, 51.5, 39.5, 38.6, 31.7, 29.6, 27.1, 26.7, 24.4, 22.4, 20.8, 14.0 ppm; FT-IR *v*_{max} 1008 (m), 1204 (s), 1368 (m), 1436 (w), 1737 (s), 2930 (w) cm⁻¹; GC-MS *R*_t 4.79 min, *m/z* 268 [M]⁺, 226 [M-Ac]⁺.

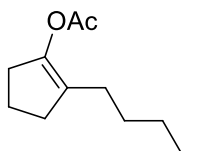
3-Methyl-2-pentylcyclopent-1-en-1-yl acetate 132



Chemical Formula: C₁₃H₂₂O₂
Molecular Weight: 210.31

Starting material obtained by organocuprate conjugate addition of 2-pentyl cyclopent-2-enone.⁶⁵ Pale yellow liquid (2 mmol scale, 375 mg, 86%), (3:1 isomer ratio, tetrasubstituted:trisubstituted double bond isomer), R_f (9:1, hexane:EtOAc) 0.6. ¹H NMR (400 MHz, CDCl₃) δ 2.70 (m, 1H), 2.45 (m, 2H), 2.16 (s, 3H), 2.15 – 1.81 (m, 2H), 1.51 – 1.22 (m, 8H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 168.8, 143.8, 130.8, 37.3, 31.7, 29.7, 29.4, 26.7, 24.4, 22.4, 20.8, 19.6, 14.0 ppm; FT-IR ν_{max} 1202 (s), 1180 (s), 1369 (w), 1756 (m), 2859 (w), 2929 (w), 2956 (w) cm⁻¹; GC-MS R_t 3.85 min, *m/z* 210 [M]⁺, 168 [M-Ac]⁺.

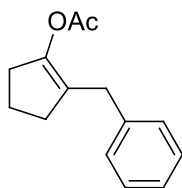
2-Pentylcyclopent-1-en-1-yl acetate⁶⁵ 87



Chemical Formula: C₁₂H₂₀O₂
Molecular Weight: 196.29

Starting material obtained by hydrogenation of 2-pentyl cyclopent-2-enone (aldol product of cyclopentanone and pentanal).¹⁴² Colourless liquid (2.5 mmol scale, 295 mg, 70%), (8:1 isomer ratio, tetrasubstituted:trisubstituted double bond isomer), R_f (9:1, hexane:EtOAc) 0.5. ¹H NMR (400 MHz, CDCl₃) δ 2.48 (m, 2H), 2.31 (m, 2H), 2.17 (s, 3H), 2.03 – 1.88 (m, 4H), 1.42 – 1.21 (m, 6H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ_C 168.9, 143.8, 126.9, 31.6, 31.1, 31.0, 26.8, 26.4, 22.5, 20.8, 19.8, 14.0 ppm; FT-IR ν_{max} 1210 (s), 1739 (s), 2859 (w), 2930 (m), 2956 (m) cm⁻¹; GC-MS R_t 3.76 min, *m/z* 196 [M]⁺, 154 [M-Ac]⁺.

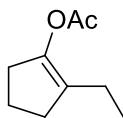
*2-Benzylcyclopent-1-en-1-yl acetate*¹⁴³ **136**



Chemical Formula: C₁₄H₁₆O₂
Molecular Weight: 216.28

Starting material obtained from 2-cyclopentylidene-1,1-dimethylhydrazine.¹⁴⁴ Colourless liquid (3.5 mmol scale, 592 mg, 78%), (2:1 isomer ratio, tetrasubstituted:trisubstituted double bond isomer), R_f (8:2, hexane:EtOAc) 0.5. ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.16 (m, 5H), 3.34 (s, 2H), 2.51 – 2.58 (m, 2H), 2.26 – 2.19 (m, 2H), 2.17 (s, 3H), 1.97 – 1.87 (m, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 169.0, 144.9, 139.0, 128.7, 128.3, 126.0, 125.9, 33.0, 31.1, 31.0, 20.8, 19.7 ppm; FT-IR ν_{max} 699 (m), 753 (m), 1205 (s), 1366 (s), 1746 (s), 2970 (m) cm⁻¹; GC-MS R_t 4.80 (major) + 4.86 min, *m/z* 216 [M]⁺, 174 [M-Ac]⁺.

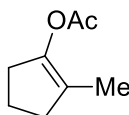
2-Ethylcyclopent-1-en-1-yl acetate **139**



Chemical Formula: C₉H₁₄O₂
Molecular Weight: 154.21

Starting material obtained from 2-cyclopentylidene-1,1-dimethylhydrazine.¹⁴⁴ Colourless oil (1 mmol scale, 115 mg, 75%), (1:1 isomer ratio, tetrasubstituted:trisubstituted double bond isomer), R_f (9:1, hexane:EtOAc) 0.5. ¹H NMR (700 MHz, CDCl₃) δ 2.47 – 2.42 (m, 2H), 2.32 – 2.28 (m, 2H), 2.13 (s, 3H), 2.01 – 1.96 (m, 2H), 1.89 (m, 2H), 0.95 (t, *J* = 7.6 Hz, 3H) ppm; ¹³C NMR (176 MHz, CDCl₃) δ_C 168.9, 143.0, 128.1, 31.0, 30.7, 21.1, 19.7, 19.6, 11.9 ppm; FT-IR ν_{max} 1178 (s), 1199 (s), 1369 (m), 1751 (m), 2971 (m) cm⁻¹; GC-MS R_t 2.99 min, *m/z* 154 [M]⁺, 112 [M-Ac]⁺.

2-Methylcyclopent-1-en-1-yl acetate 142

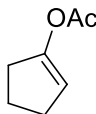


Chemical Formula: $C_8H_{12}O_2$

Molecular Weight: 140.18

Starting material obtained from 2-cyclopentylidene-1,1-dimethylhydrazine.¹⁴⁴ Colourless liquid (1 mmol scale, 74 mg, 53%), (6:1 isomer ratio, tetrasubstituted:trisubstituted double bond isomer), R_f (9:1, hexane:EtOAc) 0.5. 1H NMR (400 MHz, $CDCl_3$) δ 2.47 (m, 2H), 2.31 (m, 2H), 2.17 (s, 3H), 1.97 – 1.88 (m, 2H), 1.56 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 168.9, 143.9, 122.7, 33.5, 30.9, 20.8, 19.7, 11.9 ppm; FT-IR ν_{max} 1073 (w), 1180 (s), 1208 (s), 1369 (w), 1751 (m), 2925 (w) cm^{-1} ; GC-MS R_t 2.70 min, m/z 140 $[M]^+$, 98 $[M-Ac]^+$.

Cyclopent-1-en-1-yl acetate¹⁴⁵ 145

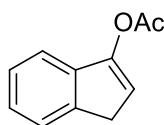


Chemical Formula: $C_7H_{10}O_2$

Molecular Weight: 126.15

Pale brown liquid (20 mmol scale, 1.90 g, 76%), R_f (8:2, hexane:EtOAc) 0.6. 1H NMR (400 MHz, $CDCl_3$) δ 5.41 (m, 1H), 2.46 (m, 2H), 2.38 (m, 2H), 2.16 (s, 3H), 1.95 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 168.7, 150.9, 113.1, 30.9, 28.6, 21.1, 21.0 ppm; FT-IR ν_{max} 1153 (w), 1201 (s), 1341 (w), 1370 (w), 1666 (w), 1755 (s), 2856 (w), 2928 (m) cm^{-1} ; GC-MS R_t 3.62 min, m/z 126 $[M]^+$, 84 $[M-Ac]^+$.

*1H-Inden-3-yl acetate*¹⁴⁶⁻¹⁴⁷ **147**

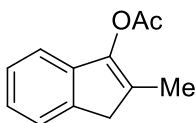


Chemical Formula: C₁₁H₁₀O₂

Molecular Weight: 174.20

White crystalline solid, m.p. 48 - 49 °C (petroleum ether), (lit. 48.5 - 49.5 °C), (1.4 mmol scale, 182 mg, 73%), R_f (9:1, hexane:EtOAc) 0.5. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, *J* = 7.3 Hz, 1H), 7.36 – 7.25 (m, 3H), 6.36 (t, *J* = 2.3 Hz, 1H), 3.45 (d, *J* = 2.4 Hz, 2H), 2.37 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 168.3, 149.1, 141.8, 139.0, 126.3, 125.7, 124.1, 118.0, 115.6, 35.0, 21.2 ppm; FT-IR ν_{max} 1007 (m), 1074 (m), 1112 (m), 1166 (m), 1207 (s), 1361 (m), 1725 (s) cm⁻¹; GC-MS R_t 4.07 min, *m/z* 174 [M]⁺, 132 [M-Ac]⁺.

*2-Methyl-1H-inden-3-yl acetate*¹⁴⁸ **149**

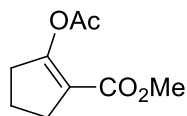


Chemical Formula: C₁₂H₁₂O₂

Molecular Weight: 188.22

Starting material obtained from 2-(2,3-dihydro-1H-inden-1-ylidene)-1,1-dimethylhydrazine.¹⁴⁴ Yellow oil (5 mmol scale, 515 mg, 55%), R_f (9:1, hexane:EtOAc) 0.4. ¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, *J* = 7.6 Hz, 1H), 7.27 (m, 1H), 7.17 (td, *J* = 7.4, 1.2 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 3.36 (s, 2H), 2.39 (s, 3H), 2.01 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 168.4, 144.4, 140.2, 139.8, 128.4, 126.2, 124.6, 123.7, 117.1, 39.1, 20.6, 12.3 ppm; FT-IR ν_{max} 715 (m), 749 (s), 1122 (m), 1197 (s), 1365 (m), 1752 (s) cm⁻¹; GC-MS R_t 4.07 min, *m/z* 188 [M]⁺, 146 [M-Ac]⁺.

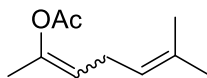
*Methyl 2-acetoxycyclopent-1-ene carboxylate*¹⁴⁹ **151**



Chemical Formula: C₉H₁₂O₄
Molecular Weight: 184.19

Colourless liquid (5 mmol scale, 680 mg, 74%), R_f (9:1, hexane:EtOAc) 0.4. ¹H NMR (400 MHz, CDCl₃) δ 3.73 (s, 3H), 2.70 – 2.61 (m, 4H), 2.25 (s, 3H), 2.01 – 1.94 (m, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 167.7, 164.1, 160.0, 118.0, 51.3, 33.5, 29.4, 20.9, 19.1 ppm; FT-IR ν_{max} 1043 (m), 1132 (m), 1174 (s), 1217 (s), 1366 (s), 1717 (s), 1739 (s), 2971 (m) cm⁻¹; GC-MS R_t 3.65 min, *m/z* 184 [M]⁺, 142 [M-Ac]⁺.

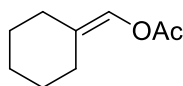
*6-Methylhepta-2,5-dien-2-yl acetate*¹⁵⁰ **152**



Chemical Formula: C₁₀H₁₆O₂
Molecular Weight: 168.23

Pale yellow liquid (20 mmol scale, 2.25 g, 67%), (~1:1 mixture of *E/Z* isomers), R_f (9:1, hexane:EtOAc) 0.4. ¹H NMR (400 MHz, CDCl₃) δ 5.14-4.75 (m, 2H), 2.74-2.20 (m, 2H), 2.18 (s, 1.5H, *E/Z*), 2.16 (s, 1.5H, *E/Z*), 1.89 (m, 3H), 1.70 (m, 3H), 1.63 (m, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 169.2, 168.9, 156.2, 144.6, 132.5, 122.9, 121.5, 115.8, 101.3, 33.4, 25.7, 25.6, 25.1, 24.5, 21.1, 20.8, 19.5, 17.7, 17.6, 15.2 ppm; FT-IR ν_{max} 1217 (s), 1370 (s), 1752 (s), 2971 (m) cm⁻¹; GC-MS R_t 3.16 + 3.29 min, *m/z* 168 [M]⁺, 126 [M-Ac]⁺.

*Cyclohexylidenemethyl acetate*¹⁵¹ **154**

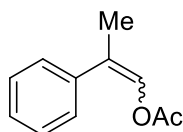


Chemical Formula: C₉H₁₄O₂

Molecular Weight: 154.21

Methanesulfonic acid (10 mol%) and 4 equivalents of isopropenyl acetate were used. Pale yellow liquid (10 mmol scale, 980 mg, 64%), R_f (9:1, hexane:EtOAc) 0.5. ¹H NMR (400 MHz, CDCl₃) δ 6.87 (t, *J* = 1.2 Hz, 1H), 2.25 (m, 2H), 2.15 (s, 3H), 2.06 (m, 2H), 1.61 – 1.48 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ_C 168.6, 127.1, 125.7, 30.6, 27.9, 26.8, 26.5, 26.2, 20.8; FT-IR ν_{max} 1204 (s), 1220 (s), 1745 (s), 2854 (w), 2927 (m) cm⁻¹; GC-MS R_t 3.27 min, *m/z* 154 [M]⁺, 112 [M-Ac]⁺.

*2-Phenylprop-1-en-1-yl acetate*¹⁵² **156**

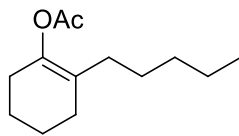


Chemical Formula: C₁₁H₁₂O₂

Molecular Weight: 176.21

Yellow liquid (10 mmol scale, 1.56 g, 89%), (3.3:1 mixture of *E*:*Z* isomers), R_f (9:1, hexane:EtOAc) 0.5. ¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.22 (m, 6H), 2.25 (s, 3H, (*E*)), 2.15 (s, 3H, (*Z*)), 2.12 (d, *J* = 1.5 Hz, 3H, (*E*)), 2.05 (d, *J* = 1.5 Hz, 3H, (*Z*)) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C *E*: 168.0, 139.1, 132.6, 128.5, 127.3, 125.8, 121.6, 20.9, 13.6 ppm; FT-IR ν_{max} 1067 (m), 1117 (s), 1209 (s), 1369 (m), 1752 (s) cm⁻¹; GC-MS R_t 3.74 + 3.91 (major) min, *m/z* 176 [M]⁺, 134 [M-Ac]⁺.

2-Pentylcyclohex-1-en-1-yl acetate¹⁵³ **158**



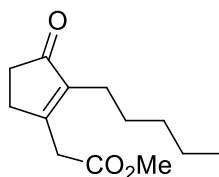
Chemical Formula: C₁₃H₂₂O₂
Molecular Weight: 210.31

Starting material obtained by hydrogenation of 2-pentylidenecyclohexanone (aldol product of cyclohexanone and pentanal). Colourless liquid (1.1 mmol scale, 135 mg, 57%), R_f (9:1, hexane:EtOAc) 0.6. ¹H NMR (400 MHz, CDCl₃) δ 2.15 (s, 3H), 2.15 – 2.06 (m, 4H), 1.92 (t, *J* = 7.7 Hz, 2H), 1.73 – 1.62 (m, 4H), 1.40 – 1.21 (m, 6H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 169.4, 141.9, 124.5, 31.7, 30.1, 27.7, 27.1, 26.9, 23.1, 22.5, 22.5, 20.9, 14.0 ppm; FT-IR ν_{max} 730 (m), 907 (m), 1111 (m), 1217 (s), 1369 (m), 1750 (s), 2930 (m) cm⁻¹; GC-MS R_t 4.03 min, *m/z* 210 [M]⁺, 168 [M-Ac]⁺.

General Procedure for the Oxidation/Bromination of Enol Acetates

For a typical 1.0 mmol scale reaction, the corresponding enol acetate was dissolved in MeCN (5 mL). Copper(II) bromide (0.45 g, 2 equiv.) was then added and the mixture was stirred under reflux until full conversion was observed (TLC). The resultant mixture was allowed to cool and after removal of MeCN *in vacuo*, was partitioned between H₂O (10 mL) and Et₂O (15 mL). The product was extracted using further Et₂O (2 x 15 mL). After drying over Na₂SO₄ and concentration *in vacuo*, the crude product was purified using SiO₂ column chromatography (hexane/EtOAc) where necessary.

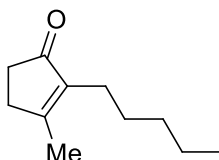
*Methyl 2-(3-oxo-2-pentylcyclopent-1-en-1-yl)acetate*¹⁵⁴ **23**



Chemical Formula: C₁₃H₂₀O₃
Molecular Weight: 224.30

Colourless liquid (1 mmol scale, 220 mg, 99%), R_f (9:1, hexane:EtOAc) 0.1. ¹H NMR (400 MHz, CDCl₃) δ 3.74 (s, 3H), 3.46 (s, 2H), 2.63 (m, 2H), 2.42 (m, 2H), 2.19 (m, 2H), 1.21-1.44 (m, 6H), 0.88 (t, *J* = 8.0 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 209.2, 169.6, 163.3, 143.3, 52.3, 36.6, 34.3, 31.8, 29.7, 28.0, 23.2, 22.5, 14.0 ppm; FT-IR ν_{max} 1171 (s), 1194 (s), 1435 (m), 1644 (m), 1698 (s), 1738 (s), 2860 (w), 2929 (w), 2954 (w) cm⁻¹; GC-MS R_t 4.70 min, *m/z* 224 [M]⁺, 193 [M-OMe]⁺, 154 [M-C₅H₁₁]⁺, 151 [M-CH₂CO₂Me]⁺.

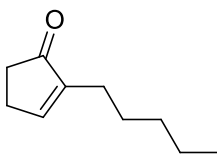
*3-Methyl-2-pentylcyclopent-2-enone*¹⁵⁵ **134**



Chemical Formula: C₁₁H₁₈O
Molecular Weight: 166.26

Colourless liquid (1 mmol scale, 75% isomerically pure starting material, 112 mg, 90%), R_f (9:1, hexane:EtOAc) 0.2. ¹H NMR (400 MHz, CDCl₃) δ 2.50 (m, 2H), 2.37 (m, 2H), 2.17 (t, *J* = 7.6 Hz, 2H), 2.06 (s, 3H), 1.43 – 1.21 (m, 6H), 0.88 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 209.7, 170.0, 140.8, 34.3, 31.8, 31.5, 28.1, 23.0, 22.5, 17.2, 14.0 ppm; FT-IR ν_{max} 1385 (w), 1645 (m), 1695 (s), 2858 (w), 2926 (w), 1956 (w) cm⁻¹; GC-MS R_t 3.89 min, *m/z* 166 [M]⁺, 151 [M-Me]⁺.

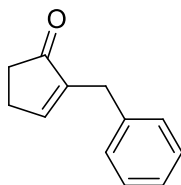
2-Pentylcyclopent-2-enone¹⁵⁵ 20



Chemical Formula: C₁₀H₁₆O
Molecular Weight: 152.23

Pale yellow liquid (1 mmol scale, 90% isomerically pure starting material, 122 mg, 89%), R_f (9:1, hexane:EtOAc) 0.2. ¹H NMR (400 MHz, CDCl₃) δ 7.31 (m, 1H), 2.60 – 2.54 (m, 2H), 2.43 – 2.38 (m, 2H), 2.17 (m, 2H), 1.54 – 1.44 (m, 2H), 1.38 – 1.24 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 210.1, 157.2, 146.6, 34.6, 31.6, 27.4, 26.4, 24.7, 22.4, 14.0 ppm; FT-IR ν_{max} 1696 (s), 2860 (w), 2926 (w), 2956 (w) cm⁻¹; GC-MS R_t 3.63 min, *m/z* 152 [M]⁺, 137 [M-Me]⁺, 123 [M-Et]⁺.

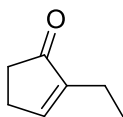
2-Benzylcyclopent-2-enone¹⁵⁶ 138



Chemical Formula: C₁₂H₁₂O
Molecular Weight: 172.22

Colourless liquid (1 mmol scale, 67% isomerically pure starting material, 22 mg, 20%), R_f (8:2, hexane:EtOAc) 0.2. ¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.20 (m, 5H), 7.17 (m, 1H), 3.51 (m, 2H), 2.56 (m, 2H), 2.50 – 2.42 (m, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 209.2, 158.8, 146.1, 138.9, 128.9, 128.5, 126.3, 34.6, 31.4, 26.5 ppm; FT-IR ν_{max} 703 (m), 790 (w), 1001 (w), 1453 (w), 1496 (w), 1695 (s) cm⁻¹; GC-MS R_t 4.37 min, *m/z* 172 [M]⁺.

2-Ethylcyclopent-2-enone¹⁵⁷ 141

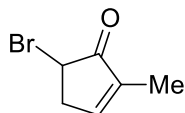


Chemical Formula: C₇H₁₀O

Molecular Weight: 110.15

Yellow liquid (1 mmol scale, 50% isomerically pure starting material, 31 mg, 62%), *R_f* (9:1, hexane:EtOAc) 0.3. ¹H NMR (400 MHz, CDCl₃) δ 7.32 (m, 1H), 2.61 – 2.55 (m, 2H), 2.45 – 2.40 (m, 2H), 2.26 – 2.17 (m, 2H), 1.12 (t, *J* = 7.5 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 210.0, 156.6, 147.9, 34.7, 26.4, 18.1, 12.1 ppm; FT-IR *v*_{max} 1262 (w), 1715 (s), 2926 (m) cm⁻¹; GC-MS *R_t* 2.67 min, *m/z* 110 [M]⁺, 95 [M-Me]⁺.

5-Bromo-2-methylcyclopent-2-enone 144

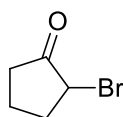


Chemical Formula: C₆H₇BrO

Molecular Weight: 175.02

Colourless liquid (1.4 mmol scale, 85% isomerically pure starting material, 35 mg, 17%), *R_f* (9:1, hexane:EtOAc) 0.2. ¹H NMR (400 MHz, CDCl₃) δ 7.33 (m, 1H), 5.11 (m, 1H), 3.07 (dd, *J* = 19.6, 6.2 Hz, 1H), 2.79 (dd, *J* = 19.6, 1.6 Hz, 1H), 1.88 (t, *J* = 1.6 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 204.7, 156.2, 143.8, 45.2, 42.1, 10.0 ppm; FT-IR *v*_{max} 918 (m), 1069 (w), 1187 (w), 1709 (s) cm⁻¹; GC-MS *R_t* 3.13 min, *m/z* 176 [M]⁺, 174 [M]⁺, 95 [M-Br]⁺; ASAP-HRMS *m/z* found [M+H]⁺ 176.9738, C₆H₈BrO requires 176.9738 (Δ = 0 ppm).

2-Bromocyclopentanone¹⁵⁸ 146

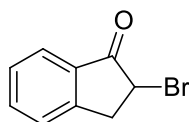


Chemical Formula: C₅H₇BrO

Molecular Weight: 163.01

Colourless liquid (1 mmol scale, 51 mg, 31%), R_f (8:2, hexane:EtOAc) 0.4. ¹H NMR (400 MHz, CDCl₃) δ 4.28 – 4.22 (m, 1H), 2.48 – 2.34 (m, 2H), 2.31 – 2.16 (m, 3H), 2.09 – 1.98 (m, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 211.2, 48.1, 35.0, 33.9, 20.2 ppm; FT-IR ν_{max} 1149 (s), 1741 (s), 2972 (w) cm⁻¹; GC-MS R_t 2.88 min, *m/z* 164 [M]⁺, 162 [M]⁺, 83 [M-Br]⁺.

2-Bromo-1-indanone¹⁵⁹ 148

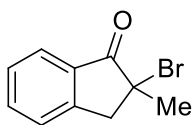


Chemical Formula: C₉H₇BrO

Molecular Weight: 211.06

Pale yellow crystalline solid, m.p. 36 - 38 °C (petroleum ether), (lit. 37 - 38 °C), (1 mmol scale, 156 mg, 74%), R_f (9:1, hexane:EtOAc) 0.2. ¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, *J* = 7.7 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.49 – 7.43 (m, 2H), 4.68 (dd, *J* = 7.5, 3.2 Hz, 1H), 3.86 (dd, *J* = 18.4, 7.7 Hz, 1H), 3.45 (dd, *J* = 18.1, 3.0 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 199.6, 151.1, 136.0, 133.6, 128.3, 126.4, 125.1, 44.1, 38.0 ppm; FT-IR ν_{max} 1208 (s), 1275 (s), 1460 (w), 1604 (m), 1717 (s) cm⁻¹; GC-MS R_t 4.35 min, *m/z* 212 [M]⁺, 210 [M]⁺, 132 [M-Br]⁺.

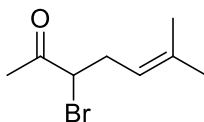
2-Bromo-2-methyl-2,3-dihydro-1H-inden-1-one¹⁶⁰ 150



Chemical Formula: C₁₀H₉BrO
Molecular Weight: 225.08

White crystalline solid, m.p. 70 - 71 °C (petroleum ether), (lit. 71 - 72 °C), (1 mmol scale, 153 mg, 68%), R_f (9:1, hexane:EtOAc) 0.3. ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.69 (td, *J* = 7.5, 1.2 Hz, 1H), 7.50 – 7.43 (m, 2H), 3.82 (d, *J* = 18.2 Hz, 1H), 3.51 (d, *J* = 18.2 Hz, 1H), 1.99 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 200.3, 149.1, 135.8, 132.7, 128.3, 126.3, 125.7, 59.5, 46.4, 26.8 ppm; FT-IR ν_{max} 1045 (m), 1212 (m), 1286 (m), 1465 (m), 1605 (m), 1715 (s) cm⁻¹; GC-MS R_t 4.27 min, *m/z* 226 [M]⁺, 224 [M]⁺, 145 [M-Br]⁺.

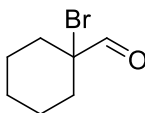
3-Bromo-6-methylhept-5-en-2-one 153



Chemical Formula: C₈H₁₃BrO
Molecular Weight: 205.09

Brown liquid (1.25 mmol scale, 117 mg, 46%), R_f (9:1, hexane:EtOAc) 0.3. ¹H NMR (400 MHz, CDCl₃) δ 4.22 (dd, *J* = 11.3, 1.5 Hz, 1H), 2.92 – 2.65 (m, 2H), 2.21 (s, 3H), 2.09 – 2.01 (m, 1H), 2.00 (s, 3H), 1.86 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 207.3, 67.9, 66.1, 42.3, 35.0, 30.1, 29.9, 28.8 ppm; FT-IR ν_{max} 1097 (s), 1370 (m), 1715 (s), 2977 (w) cm⁻¹; GC-MS R_t 4.07 min, *m/z* 207 [M+H]⁺, 205 [M+H]⁺, 125 [M-Br]⁺; ASAP-HRMS *m/z* found [M+H]⁺ 205.0221, C₈H₁₄BrO requires 205.0228 (Δ = 3.4 ppm).

*1-Bromocyclohexane carbaldehyde*¹⁶¹ **155**

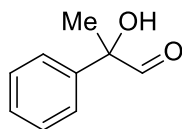


Chemical Formula: C₇H₁₁BrO

Molecular Weight: 191.07

Brown liquid (1 mmol scale, 165 mg, 86%), *R*_f (9:1, hexane:EtOAc) 0.5. ¹H NMR (400 MHz, CDCl₃) δ 9.37 (s, 1H), 2.16 – 1.96 (m, 4H), 1.88 – 1.20 (m, 6H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ_C 192.8, 71.6, 34.4, 25.0, 23.2 ppm; FT-IR *v*_{max} 1723 (s), 2858 (w), 2936 (m) cm⁻¹; GC-MS *R*_t 3.15 min, *m/z* 192 [M]⁺, 190 [M]⁺, 111 [M-Br]⁺.

*2-Hydroxy-2-phenylpropanal*¹⁶² **157**

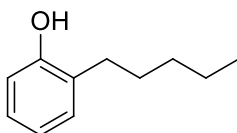


Chemical Formula: C₉H₁₀O₂

Molecular Weight: 150.17

The parent α-bromo compound (2-bromo-2-phenylpropanal) underwent hydrolysis during purification. Pale yellow oil (1.1 mmol scale, 85 mg, 57%). ¹H NMR (400 MHz, CDCl₃) δ 9.58 (s, 1H), 7.52 – 7.33 (m, 5H), 3.92 (br s, 1H), 1.73 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 199.9, 139.2, 128.9, 128.2, 125.8, 79.1, 23.6 ppm; FT-IR *v*_{max} 697 (s), 1070 (m), 1729 (m), 2982 (m), 3451 (w, br) cm⁻¹; GC-MS *R*_t 3.34 min, *m/z* 133 [M-OH]⁺, 121 [M-CHO]⁺.

*2-Pentylphenol*¹⁶³ **159**



Chemical Formula: C₁₁H₁₆O

Molecular Weight: 164.24

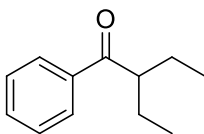
Colourless liquid (0.6 mmol scale, 42 mg, 42%), *R*_f (9:1, hexane:EtOAc) 0.2. ¹H NMR (400 MHz, CDCl₃) δ 7.16 – 7.07 (m, 2H), 6.89 (td, *J* = 7.4, 1.2 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.2 Hz,

1H), 4.81 (s, 1H), 2.63 (m, 2H), 1.71 – 1.59 (m, 2H), 1.43 – 1.33 (m, 4H), 0.96 – 0.89 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ_C 153.4, 130.2, 128.6, 127.0, 120.8, 115.2, 31.7, 29.9, 29.5, 22.6, 14.1; FT-IR ν_{max} 751 (s), 1218 (s), 1230 (s), 1367 (s), 1455 (s), 1740 (s), 2929 (m), 3430 (w, br) cm⁻¹; GC-MS R_t 3.96 min, m/z 164 [M]⁺, 107 [M-C₄H₉]⁺, 77 [C₆H₅]⁺.

Procedure for Catalytic Oxidation of 168

1,2-Bis(4-methoxyphenyl)propan-1-one (163 mg, 0.60 mmol) was dissolved in MeCN (5 mL) in a microwave vial, the solution was degassed and then saturated with O₂ *via* a balloon. Copper(II) bromide (27 mg, 0.12 mmol, 20 mol%) was then added and the vial was sealed. The solution was stirred at 85 °C under microwave irradiation for 132 h with 5 minutes of O₂ purging and monitoring by GC-MS at each of the following intervals; 24 h, 44 h, 62 h, 132 h. The solvent was then removed *in vacuo* and the product was isolated by SiO₂ column chromatography (8:2, hexane:EtOAc) as an orange oil (decomposition product (4-acetylanisole) removed under high vacuum), (92 mg, 57%).

*2-Ethyl-1-phenylbutan-1-one*¹⁶⁴ **166**

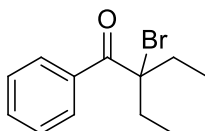


Chemical Formula: C₁₂H₁₆O
Molecular Weight: 176.25

Prepared by diethylation of acetophenone.¹⁶⁴ Colourless liquid (10 mmol scale, 650 mg, 37%), R_f (9:1, hexane:EtOAc) 0.6. ¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.97 (m, 2H), 7.61 – 7.55 (m, 1H), 7.52 – 7.46 (m, 2H), 3.33 (m, 1H), 1.89 – 1.54 (m, 4H), 0.90 (t, *J* = 7.4 Hz, 6H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ_C 204.5, 137.8, 132.8, 128.6, 128.1, 49.2, 24.9, 11.9 ppm; FT-

IR ν_{\max} 698 (s), 982 (m), 1214 (s), 1447 (m), 1677 (s), 2963 (m) cm^{-1} ; GC-MS R_t 3.85 min, m/z 176 $[\text{M}]^+$, 105 $[\text{M}-\text{C}_5\text{H}_{11}]^+$.

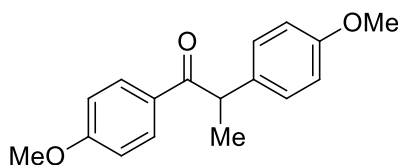
2-Bromo-2-ethyl-1-phenylbutan-1-one **167**



Chemical Formula: $\text{C}_{12}\text{H}_{15}\text{BrO}$
Molecular Weight: 255.15

Yellow liquid obtained by reaction of **166** with CuBr_2 (2 equiv.) following the general procedure in MeCN (page 127) (1.2 mmol scale, 179 mg, 58%), R_f (9:1, hexane:EtOAc) 0.6. ^1H NMR (400 MHz, CDCl_3) δ 8.07 (m, 2H), 7.58 – 7.38 (m, 3H), 2.32 (m, 4H), 0.97 (t, $J = 7.3$ Hz, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ_c 198.0, 136.6, 131.9, 129.4, 128.1, 73.2, 31.6, 9.7 ppm; FT-IR ν_{\max} 698 (s), 822 (m), 853 (m), 1229 (s), 1446 (m), 1674 (s), 2972 (w) cm^{-1} ; GC-MS R_t 4.46 min, m/z 175 $[\text{M}-\text{Br}]^+$, 105 $[\text{M}-\text{C}_5\text{H}_{11}\text{Br}]^+$; ASAP-HRMS: m/z found $[\text{M}+\text{H}]^+$ 255.0395, $\text{C}_{12}\text{H}_{16}\text{BrO}$ requires 255.0385 ($\Delta = 3.9$ ppm).

*1,2-Bis(4-methoxyphenyl)propan-1-one*¹⁶⁵ **168**

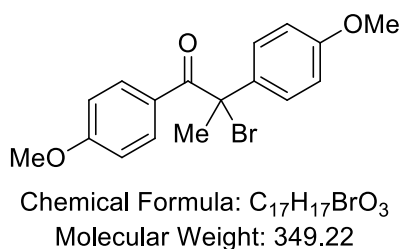


Chemical Formula: $\text{C}_{17}\text{H}_{18}\text{O}_3$
Molecular Weight: 270.32

Prepared by α -methylation of desoxyanisoin.¹⁶⁵ Thick yellow oil (10 mmol scale, 2.45 g, 91%), R_f (8:2, hexane:EtOAc) 0.3. ^1H NMR (400 MHz, CDCl_3) δ 7.99 – 7.94 (m, 2H), 7.24 – 7.19 (m, 2H), 6.90 – 6.82 (m, 4H), 4.62 (q, $J = 6.8$ Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 1.51 (d, $J = 6.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ_c 199.1, 163.1, 158.4, 134.0, 131.0, 129.5,

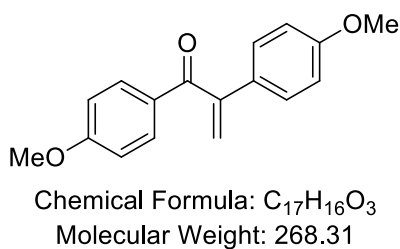
128.7, 114.3, 113.6, 55.4, 55.2, 46.6, 19.6 ppm; FT-IR ν_{\max} 780 (m), 832 (m), 952 (m), 1028 (m), 1165 (s), 1243 (s), 1509 (s), 1598 (s), 1671 (m), 2932 (w) cm^{-1} ; GC-MS R_t 6.00 min, m/z 270 $[\text{M}]^+$, 135 $[\text{MeOC}_6\text{H}_4\text{CO}]^+ + [\text{MeOC}_6\text{H}_4\text{C}_2\text{H}_4]^+$.

2-Bromo-1,2-bis(4-methoxyphenyl)propan-1-one 170



Inseparable from starting material (**168**) and unsaturated product (**169**) but observed in crude reaction mixture by ASAP-HRMS m/z found $[\text{M}+\text{H}]^+$ 349.0436, $\text{C}_{17}\text{H}_{18}\text{BrO}_3$ requires 349.0439 ($\Delta = 0.9$ ppm).

1,2-Bis(4-methoxyphenyl)prop-2-en-1-one¹⁶⁶ 169



Obtained according to procedure detailed on page 134 as an orange oil (0.6 mmol scale, 92 mg, 57%), decomposition product (4-acetylanisole) removed *in vacuo* under high vacuum, R_f (8:2, hexane:EtOAc) 0.3. ^1H NMR (400 MHz, CDCl_3) δ 7.96 – 7.93 (m, 2H), 7.40 – 7.36 (m, 2H), 6.94 – 6.87 (m, 4H), 5.92 (s, 1H), 5.47 (s, 1H), 3.88 (s, 3H), 3.82 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ_c 196.7, 163.6, 159.7, 147.8, 132.4, 129.9, 129.7, 128.1, 117.0, 114.0, 113.6, 55.5, 55.3 ppm; FT-IR ν_{\max} 783 (m), 836 (m), 979 (m), 1027 (m), 1162 (s), 1250 (s), 1508 (s),

1595 (s), 1657 (m) cm^{-1} ; GC-MS R_t 6.30 min, m/z 268 $[\text{M}]^+$, 135 $[\text{MeOC}_6\text{H}_4\text{CO}]^+$, 133 $[\text{MeOC}_6\text{H}_4\text{C}_2\text{H}_2]^+$.

Synthesis of DHH by TCCA oxidation of Hedione

Hedione (11.3 g, 50 mmol) was dissolved in MeOH (40 mL) and trichloroisocyanuric acid (TCCA), (0.58 g, 2.5 mmol, 5 mol%) was added. The mixture was stirred and heated to 50 °C in order to initiate the reaction. After initiation, the reaction was brought back to room temperature and the remainder of the TCCA (5.23 g, 22.5 mmol, 45 mol%) was added over 10 min, keeping the temperature below 30 °C. The reaction was then left to stir at r.t. for 20 h before the resultant suspension was filtered and the filtrate was concentrated *in vacuo*. The residue was purified using SiO_2 column chromatography (8:2, hexane:EtOAc) to give the pure product as a colourless liquid (5.83 g, 52%).

Batch Synthesis of DHH by SO_2Cl_2 oxidation of Hedione

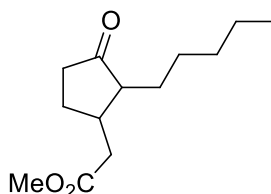
Hedione (113.0 g, 0.50 mol) was dissolved in CHCl_3 (110 mL) and sulfuryl chloride (40.4 mL, 1.1 equiv.) was added slowly, keeping the reaction below 30 °C. The reaction was then left to stir at r.t. for 2 h before MeOH (100 mL) was added. The resultant mixture was then stirred for 3 h before the solvents were removed under reduced pressure. To the residue, saturated aqueous Na_2CO_3 (200 mL) was added and the mixture was then stirred for 16 h at r.t. before the product was extracted with EtOAc (2 x 200 mL). After concentration of the organic layers *in vacuo* the resultant liquid was purified using vacuum distillation (1 mbar, 100-110 °C) to give the product as a colourless liquid (86.2 g, 77%).

Flow Synthesis of DHH by SO_2Cl_2 oxidation of Hedione

A solution of SO_2Cl_2 (1.45 M in CHCl_3) and neat Hedione were directed into a Uniqsis 0.27 mL mixing chip at 0.682 mL/min and 0.201 mL/min respectively where they were merged.

The outlet of the mixing chip was directed into a 52 mL reactor coil at r.t. ($R_t = 1$ h) and collected from the exit of the reactor into a stirred round-bottom flask (collection time 8 h). A 35 min sample was collected separately and then MeOH (7 mL) was added and the mixture was stirred at r.t. for 16 h. The solvents were removed *in vacuo* and saturated aqueous Na_2CO_3 (20 mL) was added to the residue, the mixture was then stirred for 20 h at r.t. and the product was extracted with EtOAc (2 x 20 mL). After concentration of the organic layers *in vacuo* the resultant liquid was purified using SiO_2 column chromatography (8:2, hexane:EtOAc) to give the pure product as a colourless liquid (5.06 g, 72%).

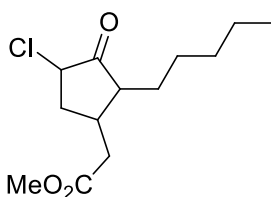
*Methyl dihydrojasmonate (Hedione)*¹⁶⁷ **14**



Chemical Formula: $\text{C}_{13}\text{H}_{22}\text{O}_3$
Molecular Weight: 226.31

R_f (8:2, hexane:EtOAc) 0.4. ^1H NMR (400 MHz, CDCl_3): δ 3.72 (3H, s), 2.65 (1H, m), 2.12-2.35 (5H, m), 1.82 (2H, m), 1.55 (2H, m), 1.30 (6H, m), 0.89 (3H, t, $J = 7.7$ Hz) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ_c 219.3 172.7, 54.2, 51.7, 39.0, 38.1, 37.7, 32.1, 27.8, 27.2, 26.3, 22.5, 14.0 ppm; FT-IR: ν_{max} 1167 (m), 1436 (w), 1734 (s), 2928 (w); GC-MS R_t 4.48 min, m/z 226 $[\text{M}]^+$.

Methyl 2-(4-chloro-3-oxo-2-pentylcyclopentyl)acetate **314**



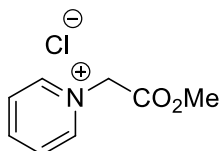
Chemical Formula: $\text{C}_{13}\text{H}_{21}\text{ClO}_3$
Molecular Weight: 260.76

R_f (9:1, hexane:EtOAc) 0.3. ¹H NMR (400 MHz, CDCl₃) δ 4.45 (d, *J* = 6.7 Hz, 1H), 3.76 (s, 3H), 3.10 – 3.00 (m, 1H), 2.75 (dd, *J* = 16.3, 4.4 Hz, 1H), 2.57 – 1.88 (m, 4H), 1.56 – 1.12 (m, 8H), 0.97 – 0.79 (m, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 202.7, 171.8, 74.7, 54.0, 52.0, 38.0, 35.8, 35.5, 34.2, 31.8, 24.6, 22.3, 13.9 ppm; FT-IR ν_{max} 998 (w), 1173 (m), 1284 (m), 1377 (w), 1436 (m), 1739 (s), 1768 (s), 2955 (m); GC-MS R_t 4.96 min, *m/z* 260 [M]⁺.

Batch Hydrogenation of DHH

Dehydrohedione (2.00 g, 8.9 mmol) was dissolved in degassed EtOH (7 mL) and 10% palladium on carbon (100 mg, 5 wt%) was added. The reaction was then purged with H₂ for 2 min. and the reaction then stirred under a H₂ atmosphere supplied by a balloon for 5 hours. The resultant mixture was passed through a short plug of SiO₂ to remove residual Pd/C. The solvent was then removed *in vacuo* to leave the product as a colourless liquid and a 1:1 mixture of *cis:trans* diastereoisomers (1.99 g, 99%).

*1-(2-Methoxy-2-oxoethyl)pyridinium chloride*⁶⁶ **96**

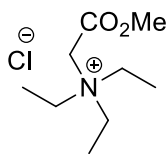


Chemical Formula: C₈H₁₀ClNO₂
Molecular Weight: 187.62

A mixture of pyridine (4.03 mL, 50 mmol) and methyl chloroacetate (4.39 mL, 50 mmol) in EtOAc (12 mL) were stirred at 80 °C for 24 h. The precipitate was collected by suction filtration and washed with EtOAc (20 mL) and Et₂O (20 mL) and then dried under high vacuum to give a white, crystalline solid (5.28 g, 56%), m.p. 173-175 °C (dec.), (Lit: 178-180 °C).⁶⁶

^1H NMR (400 MHz, DMSO- d_6) δ 9.16 – 9.06 (m, 2H), 8.77 – 8.67 (m, 1H), 8.30 – 8.21 (m, 2H), 5.74 (s, 2H), 3.78 (s, 3H) ppm; ^{13}C NMR (176 MHz, DMSO- d_6) δ 166.9, 146.8, 146.3, 127.9, 60.2, 53.1 ppm; FT-IR ν_{max} 717 (s), 795 (s), 980 (s), 1193 (s), 1216 (s), 1229 (s), 1368 (m), 1439 (m), 1489 (s), 1635 (m), 1739 (m), 2945 (m), 3021 (m), 3046 (m) cm^{-1} ; ESI-HRMS: m/z found $[\text{M-Cl}]^+$ 152.0718, $\text{C}_8\text{H}_{10}\text{NO}_2$ requires 152.0706 ($\Delta = 7.9$ ppm).

Triethyl-(2-methoxy-2-oxidanylidene-ethyl)azanium chloride **100**

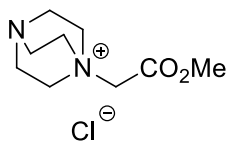


Chemical Formula: $\text{C}_9\text{H}_{20}\text{ClNO}_2$
Molecular Weight: 209.71

A mixture of triethylamine (6.97 mL, 50 mmol) and methyl chloroacetate (4.39 mL, 50 mmol) in EtOAc (12 mL) was stirred at 80 °C for 24 h. The solvent was removed under reduced pressure and the residue was dried under high vacuum to give a dark brown, viscous liquid (3.12 g, 30%).

^1H NMR (400 MHz, DMSO- d_6) δ 4.35 (s, 2H), 3.76 (s, 3H), 3.48 (q, $J = 7.3$ Hz, 6H), 1.21 (t, $J = 7.3$ Hz, 9H) ppm; ^{13}C NMR (101 MHz, DMSO- d_6) δ 165.3, 54.9, 53.9, 53.0, 7.4 ppm; FT-IR ν_{max} 999 (m), 1034 (m), 1161 (m), 1218 (s), 1399 (m), 1445 (m), 1740 (s), 2982 (m) cm^{-1} ; ESI-HRMS: m/z found $[\text{M-Cl}]^+$ 174.1479, $\text{C}_9\text{H}_{20}\text{NO}_2$ requires 174.1489 ($\Delta = 5.7$ ppm).

Methyl 2-(1-aza-4-azoniabicyclo[2.2.2]octan-4-yl)ethanoate chloride **97**

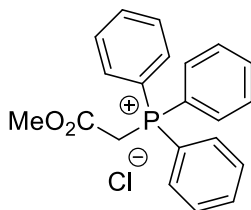


Chemical Formula: $\text{C}_9\text{H}_{17}\text{ClN}_2\text{O}_2$
Molecular Weight: 220.70

A mixture of DABCO (5.61 g, 50 mmol) and methyl chloroacetate (4.39 mL, 50 mmol) in EtOAc (12 mL) were stirred at 80 °C for 1 h. The precipitate was collected by suction filtration and washed with EtOAc (20 mL) and Et₂O (20 mL) and then dried under high vacuum to give a white solid (10.03 g, 91%), m.p. 286 - 291 °C (dec.).

¹H NMR (400 MHz, DMSO-*d*₆) δ 4.46 (s, 2H), 3.76 (s, 3H), 3.57 – 3.48 (m, 6H), 3.12 – 3.03 (m, 6H) ppm; ¹³C NMR (101 MHz, DMSO-*d*₆) δ 164.9, 60.6, 52.8, 52.2, 44.4 ppm; FT-IR ν_{max} 996 (m), 1058 (m), 1124 (s), 1214 (s), 1434 (m), 1461 (m), 1746 (s), 2911 (m) cm⁻¹; ESI-HRMS: *m/z* found [M-Cl]⁺ 185.1298, C₉H₁₇N₂O₂ requires 185.1285 (Δ = 7.0 ppm).

(Methoxycarbonylmethyl)triphenyl-phosphonium chloride¹⁶⁸ **102**



Chemical Formula: C₂₁H₂₀ClO₂P

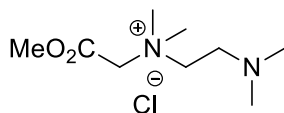
Molecular Weight: 370.81

A mixture of triphenylphosphine (13.12 g, 50 mmol) and methyl chloroacetate (4.39 mL, 50 mmol) in EtOAc (12 mL) were stirred at 80 °C for 1 h. The precipitate was collected by suction filtration and washed with EtOAc (20 mL) and Et₂O (20 mL) and then dried under high vacuum to give a white solid (8.69 g, 47%), m.p. 155 - 159 °C, (Lit: 152 - 153 °C)¹⁶⁸.

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.94 – 7.86 (m, 3H), 7.86 – 7.73 (m, 12H), 5.44 (d, *J* = 14.4 Hz, 1H), 3.60 (s, 3H) ppm; ¹³C NMR (101 MHz, DMSO-*d*₆) δ 165.5 (d, *J* = 3.5 Hz), 135.1 (d, *J* = 3.1 Hz), 133.7 (d, *J* = 10.8 Hz), 130.1 (d, *J* = 13.0 Hz), 118.2 (d, *J* = 89.0 Hz), 53.3, 29.4 (d, *J* = 57.6 Hz) ppm; FT-IR ν_{max} 881 (s), 997 (m), 1111 (s), 1199 (s), 1319 (s), 1442 (s), 1723

(s), 2736 (w), 2801 (m), 3007 (w) cm^{-1} ; ESI-HRMS: m/z found $[\text{M}-\text{Cl}]^+$ 335.1195, $\text{C}_{21}\text{H}_{20}\text{O}_2\text{P}$ requires 335.1195 ($\Delta = 0$ ppm).

*2-(Dimethylamino)ethyl-(2-methoxy-2-oxidanylidene-ethyl)-dimethyl-azanium chloride*¹⁶⁹ **98**

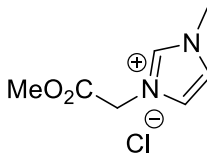


Chemical Formula: $\text{C}_9\text{H}_{21}\text{ClN}_2\text{O}_2$
Molecular Weight: 224.73

A mixture of *N,N,N',N'*-tetramethylethylenediamine (7.50 mL, 50 mmol) and methyl chloroacetate (4.39 mL, 50 mmol) in EtOAc (12 mL) were stirred at 80 °C for 1 h. The precipitate was collected by suction filtration and washed with EtOAc (20 mL) and Et_2O (20 mL) and then dried under high vacuum to give a white solid (9.57 g, 91%), m.p. 133 - 137 °C, (Lit: 116 - 118 °C).¹⁶⁹

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.48 (s, 2H), 3.73 (s, 3H), 3.65 – 3.58 (m, 2H), 3.28 (s, 6H), 2.67 – 2.59 (m, 2H), 2.14 (s, 6H) ppm; ^{13}C NMR (101 MHz, $\text{DMSO}-d_6$) δ 165.2, 60.5, 60.4, 52.5, 52.3, 52.1, 44.7 ppm; FT-IR ν_{max} 878 (s), 921 (m), 994 (s), 1037 (s), 1138 (m), 1194 (s), 1209 (s), 1232 (s), 1243 (s), 1426 (m), 1448 (s), 1737 (s), 1746 (s), 2769 (m) cm^{-1} ; ESI-MS m/z 189 $[\text{M}-\text{Cl}]^+$.

*Methyl 2-(3-methyl-1H-imidazolium-1-yl)acetate chloride*¹⁷⁰ **101**



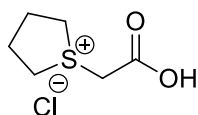
Chemical Formula: $\text{C}_7\text{H}_{11}\text{ClN}_2\text{O}_2$
Molecular Weight: 190.63

A mixture of 1-methylimidazole (3.99 mL, 50 mmol) and methyl chloroacetate (4.39 mL, 50 mmol) in EtOAc (12 mL) were stirred at 80 °C for 1 h. The precipitate was collected by suction

filtration and washed with EtOAc (20 mL) and Et₂O (20 mL) and then dried under high vacuum to give a pale brown solid (4.25 g, 45%), m.p. 119 - 121 °C.

¹H NMR (400 MHz, DMSO-*d*₆) δ 9.37 (s, 1H), 7.85 – 7.78 (m, 2H), 5.38 (s, 2H), 3.93 (s, 3H), 3.73 (s, 3H) ppm; ¹³C NMR (101 MHz, DMSO-*d*₆) δ 167.4, 137.8, 123.7, 123.4, 52.8, 49.4, 35.95 ppm; FT-IR ν_{max} 983 (m), 1030 (m), 1176 (s), 1218 (s), 1369 (m), 1426 (m), 1568 (m), 1753 (s), 2961 (m), 3003 (m), 3098 (m), cm⁻¹; ESI-HRMS: *m/z* found [M-Cl]⁺ 155.0811, C₇H₁₁N₂O₂ requires 155.0815 (Δ = 2.6 ppm).

1-(Carboxymethyl)tetrahydrothiophenium chloride **312**



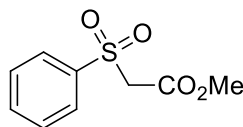
Chemical Formula: C₆H₁₁ClO₂S

Molecular Weight: 182.67

At 0 °C, methyl chloroacetate (7.08 mL, 100 mmol) and tetrahydrothiophene (4.41 mL, 50 mmol) were added to H₂O (5 mL). The mixture was stirred at 80 °C for 2 h and then concentrated *in vacuo*. The residue was dried under high vacuum to give a viscous yellow liquid (5.02 g, 55%). A yellow solid was obtained following flash SiO₂ column chromatography (2:1 DCM:MeOH), m.p. 119 - 124 °C.

¹H NMR (400 MHz, DMSO-*d*₆) δ 4.47 (s, 2H), 3.60 – 3.42 (m, 4H), 2.30 – 2.05 (m, 4H) ppm; ¹³C NMR (101 MHz, DMSO-*d*₆) δ 166.8, 45.1, 43.1, 28.1 ppm; FT-IR ν_{max} 919 (s), 950 (m), 1239 (s), 1313 (m), 1373 (m), 1393 (m), 1424 (m), 1706 (s), 2325 (m), 2946 (m) cm⁻¹; ESI-HRMS: *m/z* found [M-Cl]⁺ 147.0470, C₆H₁₁O₂S requires 147.0474 (Δ = 2.7 ppm).

*Methyl 2-(phenylsulfonyl)acetate*¹⁷¹ **99**

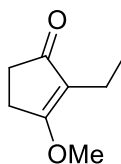


Chemical Formula: C₉H₁₀O₄S
Molecular Weight: 214.24

Tetrabutylammonium iodide (1 g, 2.7 mmol), KI (9.96 g, 60 mmol) and methyl bromoacetate (5.68 mL, 60 mmol) were added to MeOH (30 mL) followed by sodium benzenesulfinate (8.21 g, 50 mmol). The mixture was stirred at 25 °C for approximately 72 h, after which time the volatile materials were removed under reduced pressure and the product extracted with Et₂O. The Et₂O layers were combined and dried over Na₂SO₄, filtered and concentrated *in vacuo* to give a brown liquid (11.62 g). 3 g were purified by flash SiO₂ column chromatography (7:3 hexane:EtOAc) to give a pale yellow liquid (2.35 g, 85%).

¹H NMR (400 MHz, CDCl₃) δ 8.01 – 7.91 (m, 2H), 7.75 – 7.65 (m, 1H), 7.65 – 7.54 (m, 2H), 4.13 (s, 2H), 3.71 (s, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 162.9, 138.8, 134.5, 129.4, 128.7, 61.0, 53.2 ppm; FT-IR ν_{max} 999 (m), 1083 (s), 1148 (s), 1280 (s), 1310 (s), 1324 (s), 1436 (m), 1448 (m), 1586 (w), 1739 (s), 2955 (w) cm⁻¹; GC-MS: R_t 4.67 min, *m/z* 215 [M+H]⁺.

*2-Ethyl-3-methoxycyclopent-2-enone*¹⁷² **103**



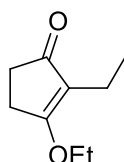
Chemical Formula: C₈H₁₂O₂
Molecular Weight: 140.18

To a solution of 2-ethyl-1,3-cyclopentanedione (3.15 g, 25.0 mmol) in MeOH (50 mL) was added *p*-TSA (0.48 g, 2.5 mmol, 10 mol%). The resultant mixture was stirred under reflux for

6 h and then at r.t. for 3 days. After concentration *in vacuo* the crude product was purified using SiO₂ column chromatography (95:5, DCM:MeOH) to give a colourless liquid (1.82 g, 52%).

¹H NMR (400 MHz, CDCl₃) δ 3.95 (s, 3H), 2.66 (m, 2H), 2.44 (m, 2H), 2.15 (q, *J* = 8.6 Hz, 2H), 0.99 (t, *J* = 7.6 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 204.8, 184.3, 122.2, 56.3, 33.5, 24.5, 14.5, 12.6 ppm; FT-IR ν_{max} 616 (w), 913 (m), 1015 (m), 1058 (m), 1123 (m), 1267 (s), 1356 (s), 1464 (m), 1616 (s), 1683 (m), 2934 (w); GC-MS *R*_t 3.68 min, *m/z* 140 [M]⁺, 125 [M-Me]⁺.

*3-Ethoxy-2-ethylcyclopent-2-enone*¹⁷³ **313**



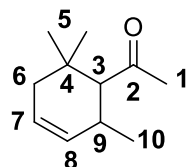
Chemical Formula: C₉H₁₄O₂
Molecular Weight: 154.21

Synthesis performed according to the above synthesis of 2-ethyl-3-methoxycyclopent-2-enone **103** but with EtOH solvent on 20.0 mmol scale. Crude product purified using SiO₂ column chromatography (95:5, DCM:MeOH) to give a colourless liquid (1.81 g, 59%).

¹H NMR (400 MHz, CDCl₃) δ 4.24 (q, *J* = 7.1 Hz, 2H), 2.68 – 2.64 (m, 2H), 2.46 – 2.44 (m, 2H), 2.17 (q, *J* = 6.6 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 205.0, 184.1, 122.1, 65.0, 33.5, 24.9, 15.3, 14.6, 12.6 ppm; FT-IR ν_{max} 862 (m), 1028 (m), 1128 (m), 1232 (m), 1264 (s), 1350 (s), 1377 (s), 1615 (s), 1684 (m), 2933 (w, br); GC-MS *R*_t 3.79 min, *m/z* 154 [M]⁺, 125 [M-Et]⁺.

4.3. δ -Damascone

1-(2,6,6-Trimethylcyclohex-3-en-1-yl)ethanone (Isofloriffone) **45/46**



Chemical Formula: C₁₁H₁₈O
Molecular Weight: 166.26

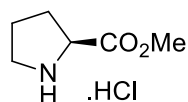
AlCl₃ catalysed: Mesityl oxide (1.00 g, 10.0 mmol) was dissolved in 1-nitropropane (2 mL) and stirred at 5 °C before aluminium(III) chloride (0.90 g, 75 mol%) was added. The mixture was stirred for a further 5 min and then piperylene (44% *trans*), (2.70 g, ~ 1.5 eq.) was added drop-wise. The reaction was stirred at 5 °C for a further 5 min and then allowed to warm to room temperature, at which point it was stirred for a further 3 h. The reaction mixture was then washed with 10% aqueous Na₂SO₄ (3 x 30 mL) and concentrated *in vacuo* to leave a brown oil. The pure product was then obtained by SiO₂ column chromatography (9:1, hexane:EtOAc) as a colourless liquid (440 mg, 26%).

Chloroaluminate ionic liquid catalysed: The chloroaluminate butylmethylimidazolium ionic liquid ([Bmim]Cl(AlCl₃)_{1.5}) (0.37 g, 1.0 mmol) was transferred to a dry vessel and charged with a nitrogen atmosphere. Mesityl oxide (0.10 g, 1.0 mmol) was added to the stirring liquid at room temperature followed by drop-wise addition of piperylene (44% *trans*) (0.27g, ~ 1.5 eq.). The mixture was then stirred at 40 °C for 18 h after which time H₂O (10 mL) was added and the product was extracted using Et₂O (2 x 10 mL). The solvent was removed *in vacuo* and then the samples were submitted for GC-MS analysis and yield estimation using *n*-pentadecane as an internal standard.

Spectral data reported corresponds to *trans*-isofloriffone **46**

^1H NMR (700 MHz, CDCl_3) δ 5.53 – 5.50 (m, 1H, **7**), 5.45 – 5.42 (m, 1H, **8**), 2.52 – 2.44 (m, 1H, **9**), 2.28 (d, J = 10.6 Hz, 1H, **3**), 2.18 (s, 3H, **1**), 1.98 – 1.93 (m, 1H, **6**), 1.71 – 1.65 (m, 1H, **6**), 0.97 (s, 3H, **5**), 0.91 (s, 3H, **5**), 0.87 (d, J = 7.0 Hz, 3H, **10**) ppm; ^{13}C NMR (176 MHz, CDCl_3) δ 213.2 (**2**), 131.7 (**8**), 124.1 (**7**), 63.4 (**3**), 41.7 (**6**), 34.7 (**1**), 32.8 (**4**), 31.5 (**9**), 29.7 (**5**), 20.6 (**5**), 19.8 (**5**) ppm; FT-IR: ν_{max} 713 (m), 966 (w), 1119 (w), 1154 (m), 1366 (m), 1457 (w), 1710 (s), 2958 (m); GC-MS R_t 3.04 min, m/z 166 $[\text{M}]^+$; ASAP-HRMS: m/z found $[\text{M}+\text{H}]^+$ 167.1431, $\text{C}_{11}\text{H}_{19}\text{O}$ requires 167.1436 (Δ = 3.0 ppm).

(*S*)-Methyl pyrrolidine-2-carboxylate hydrochloride¹⁷⁴ **190**

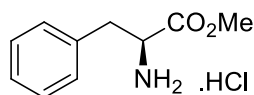


Chemical Formula: $\text{C}_6\text{H}_{12}\text{ClNO}_2$
Molecular Weight: 165.62

L-proline (4.61 g, 40 mmol) was dissolved in dry methanol (40 mL) and stirred under an N_2 atmosphere at $-10\text{ }^\circ\text{C}$. Thionyl chloride (12.0 mL, 165 mmol, 4.1 equiv.) was added drop-wise over 5 min and the mixture was left to stir for 30 min at $-10\text{ }^\circ\text{C}$. The ice bath was then removed and the reaction was left to stir at r.t. for a further 2 days. The solvent was then removed *in vacuo* and the remaining pale green liquid was dissolved in more methanol (20 mL) and concentrated *in vacuo*. This was repeated twice more to leave a pale green gum which was triturated with hexane (3 x 15 mL) to leave the product as a white solid (6.48 g, 98%).

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.81 (s, br, 2H) 4.35 (t, J = 4.5 Hz, 1H), 3.76 (s, 3H), 3.26 – 3.15 (m, 2H), 2.30 – 2.21 (m, 1H), 2.04 – 1.87 (m, 3H) ppm; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ_c 169.6, 58.8, 53.4, 45.6, 28.2, 23.3 ppm; FTIR: ν_{max} 918 (m), 1058 (m), 1744 (s), 2558 (w), 2728 (w), 2855 (w); ESI-MS: m/z 130 $[\text{M}]^+$.

(S)-Methyl 2-amino-3-phenylpropanoate hydrochloride¹⁷⁵ **315**

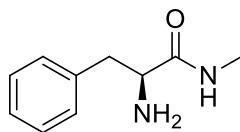


Chemical Formula: C₁₀H₁₄ClNO₂

Molecular Weight: 215.68

Prepared in the same way as above (**190**) but from L-phenylalanine. Isolated as a white solid (8.39 g, 97%), m.p. 158 - 162 °C, (lit. 158 – 160 °C). ¹H NMR (400 MHz, DMSO-d₆): δ 8.73 (s, br, 3H), 7.36 – 7.23 (m, 5H), 4.05 – 3.96 (m, 1H), 3.66 (s, 3H), 3.23 – 3.08 (m, 2H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ_C 169.8, 135.1, 129.9, 129.1, 127.7, 53.7, 53.0, 36.3 ppm; FT-IR: ν_{max} 702 (s), 741 (s), 1084 (m), 1146 (m), 1215 (m), 1239 (s), 1496 (m), 1744 (s), 2841 (w); ESI-MS: *m/z* 180 [M]⁺.

(S)-2-Amino-N-methyl-3-phenylpropanamide¹⁷⁶ **316**



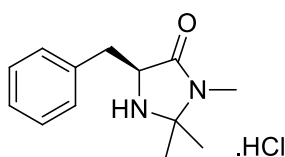
Chemical Formula: C₁₀H₁₄N₂O

Molecular Weight: 178.23

Methylamine solution (33%, w/w, in EtOH) (13.5 mL, 46 mmol, 4 eq.) was stirred in ethanol (20 mL) at 0 °C and (*S*)-methyl 2-amino-3-phenylpropanoate hydrochloride (2.50 g, 11.5 mmol) was added. The mixture was stirred at 0 °C for 30 min and then allowed to warm to r.t. after which time it was left to stir for 2 days. The solvent was removed *in vacuo* to leave an oil which was treated with Et₂O (3 x 20 mL) and concentrated under reduced pressure to remove any residual NH₂Me. The resultant oil was treated with aqueous saturated NaHCO₃ (20 mL), extracted with DCM (3 x 15 mL), dried over Na₂SO₄ and concentrated again to leave a pale yellow oil which was left under high-vacuum to leave the free amine as a slightly off white solid (4.78 g, 82%), m.p. 67 - 69 °C (lit. 67 – 69 °C).

^1H NMR (400 MHz, DMSO- d_6): δ 7.78 (s, br, 1H), 7.30 – 7.18 (m, 5H), 3.35 – 3.32 (m, 1H), 2.94 – 2.89 (m, 1H), 2.62 – 2.58 (m, 1H), 2.57 (d, J = 5.3 Hz, 3H), 1.62 (s, br, 2H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 175.2, 139.4, 129.7, 128.5, 126.5, 56.9, 41.7, 25.9 ppm; FT-IR: ν_{max} 699 (s), 745 (s), 1109 (m), 1398 (m), 1520 (s), 1644 (s), 2915 (w), 3344 (w); ESI-MS: m/z 180 $[\text{M}]^+$.

(*S*)-5-Benzyl-2,2,3-trimethylimidazolidin-4-one hydrochloride¹⁷⁷ **187**

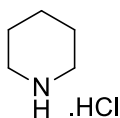


Chemical Formula: $\text{C}_{13}\text{H}_{19}\text{ClN}_2\text{O}$
Molecular Weight: 254.76

(*S*)-2-Amino-*N*-methyl-3-phenylpropanamide (1.40 g, 7.9 mmol) was dissolved in methanol (20 mL) and acetone (3.0 mL, 5 eq.) and then *p*-TSA (0.023 g, 1.5 mol%) was added. The reaction was left to stir under N_2 for 18 h, after which time the solvent was removed under reduced pressure. The resultant mixture was dissolved in Et_2O (20 mL) and treated with the appropriate amount of HCl (2 M in Et_2O , 4.0 mL) to give the hydrochloride salt which was recrystallized from IPA to give the product as an off white crystalline solid (1.68 g, 83%), m.p. 161 - 164 $^\circ\text{C}$ (lit. 155 – 158 $^\circ\text{C}$).

^1H NMR (400 MHz, DMSO- d_6): δ 10.68 (s, br, 2H), 7.50 – 7.27 (m, 5H), 4.59 (s, 1H), 3.40 – 3.23 (m, 2H), 2.79 (s, 3H), 1.71 (s, 3H), 1.51 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6): δ_{C} 167.0, 136.8, 129.8, 127.4, 77.2, 57.8, 33.5, 25.3, 24.1, 22.3 ppm; FT-IR: ν_{max} 611 (s), 697 (s), 753 (m), 1057 (m), 1269 (m), 1393 (s), 1422 (m), 1594 (w), 1722 (s), 2487 (w), 2546 (w), 2682 (m); ESI-MS: m/z 219 $[\text{M}]^+$.

*Piperidine hydrochloride*¹⁷⁸ **192**



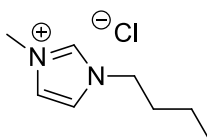
Chemical Formula: C₅H₁₂ClN

Molecular Weight: 121.61

Piperidine (2.00 g, 23.5 mmol) was stirred in diethyl ether (10 mL) at 0 °C and HCl (2M in ether) (6.0 mL, 1.0 eq.) was added slowly over 10 min. A white precipitate formed and the mixture was left to stir for a further 20 min before this was collected by filtration. The solid was washed with Et₂O (2 x 10 mL) leaving the product as a white solid (2.82 g, 99%), m.p. 246 - 249 °C (lit. 245 – 247 °C).

¹H NMR (400 MHz, DMSO-d₆): δ 9.08 (s, br, 2H), 2.96 (t, *J* = 5.6 Hz, 4H), 1.70 – 1.65 (m, 4H), 1.57 – 1.51 (m, 2H) ppm; ¹³C NMR (100 MHz, DMSO-d₆): δ_C 43.9, 22.5, 22.2 ppm; FT-IR: ν_{max} 942 (m), 1460 (m), 1592 (m), 2526 (s), 2732 (s), 2801 (s), 2940 (s); ESI-MS: *m/z* 85 [M]⁺.

1-Butyl-3-methylimidazolium chloride ([Bmim]Cl)¹⁷⁹ **196**



Chemical Formula: C₈H₁₅ClN₂

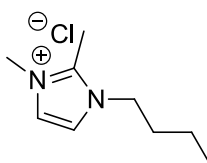
Molecular Weight: 174.67

N-Methylimidazole (20.00 g, 240 mmol) was dissolved in acetonitrile (15 mL) and stirred at room temperature in oven dried glassware. 1-Chlorobutane (22.55 g, 250 mmol) was added and the mixture was left to stir under reflux for 48 h under a nitrogen atmosphere. This left a thick liquid which was concentrated under reduced pressure and washed with ethyl acetate (3

x 15 mL) (top layer decanted each time). The residue was dried under high vacuum to leave the title compound as a clear liquid (41.12 g, 94%).

^1H NMR (400 MHz, DMSO- d_6): δ 11.04 (s, 1H), 7.32 (t, J = 1.8 Hz, 1H), 7.26 (t, J = 1.8 Hz, 1H), 4.35 (t, J = 7.8 Hz, 2H), 4.15 (s, 3H), 1.96 – 1.88 (m, 2H), 1.42 (dt, J = 7.3 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 138.8, 123.0, 121.4, 49.9, 36.6, 32.2, 19.5, 13.4 ppm; FT-IR: ν_{max} 756 (m), 1170 (s), 1465 (w), 1570 (m), 2956 (m); ESI-MS: m/z 138 $[\text{M}]^+$.

1-Butyl-2,3-dimethylimidazolium chloride ([DBmim]Cl)¹⁸⁰ **197**



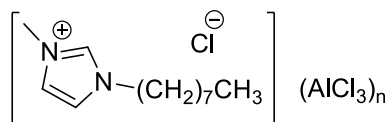
Chemical Formula: $\text{C}_9\text{H}_{17}\text{ClN}_2$
Molecular Weight: 188.70

1,2-Dimethylimidazole (10.00 g, 104 mmol) was dissolved in acetonitrile (15 mL) and stirred at room temperature in oven dried glassware. 1-Chlorobutane (10.18 g, 110 mmol) was added and the mixture was left to stir under reflux for 48 h in a nitrogen atmosphere. This left a thick liquid which was concentrated under reduced pressure and washed with ethyl acetate (3 x 15 mL) (top layer decanted each time) and dried under high vacuum to leave the title compound as a pale orange solid (11.05 g, 56%).

^1H NMR (400 MHz, DMSO- d_6): δ 7.68 (d, J = 2.1 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H), 4.12 (t, J = 7.3 Hz, 2H), 3.76 (s, 3H), 2.59 (s, 3H), 1.72 – 1.64 (m, 2H), 1.33 – 1.24 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H), ppm; ^{13}C NMR (100 MHz, CDCl_3): δ_{C} 144.7, 122.8, 121.3, 47.7, 35.1, 31.7, 19.4,

13.9, 9.6 ppm; FT-IR: ν_{\max} 758(s), 822 (s), 1116 (m), 1139 (m), 1244 (m), 1275 (m), 1420 (m), 1459 (m), 1539 (m), 2935 (m), 3027 (m); ESI-MS: m/z 154 $[M]^+$, 139 $[M-Me]^+$.

Chloro-aluminate ionic liquids ([O_{mim}]Cl (AlCl₃)₁) **199**



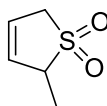
Chemical Formula: C₁₂H₂₃ClN₂

Molecular Weight: 230.78

1-Methyl-3-octyl imidazolium chloride (2.62 g, 11.4 mmol) was stirred in an oven dried 2-necked round bottom flask under a stream of nitrogen at 50 °C. Anhydrous aluminium(III) chloride (1.51 g, 1.0 equiv.) was then added portion-wise over 5 min and the temperature was raised to 100 °C, the resultant mixture was left to stir vigorously under N₂ for 2 h until all the AlCl₃ had dissolved. The product was allowed to cool to room temperature leaving a slightly less viscous dark yellow liquid. (4.08 g, 99%).

¹H NMR (400 MHz, CDCl₃): δ 8.84 (s, 1H), 7.35 (s, 1H), 7.32 (s, 1H), 4.24 (t, J = 7.5 Hz, 2H), 4.04 (s, 3H), 1.94 (t, J = 7.3 Hz, 2H), 1.24-1.39 (m, 10H) 0.91 (t, J = 3.4 Hz, 3H), ppm; ¹³C NMR (100 MHz, CDCl₃): δ_C 135.6, 123.8, 122.4, 50.6, 37.0, 31.7, 30.1, 29.0, 28.9, 26.2, 22.6, 14.1 ppm; FT-IR: ν_{\max} 772 (m), 1169 (s), 1466 (m), 1570 (m), 2854 (m), 2924 (s), 3050 (m); ESI-MS: m/z 197 $[M]^+$.

Piperylene sulfone¹⁸¹ **317**

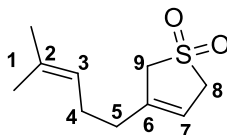


Chemical Formula: C₅H₈O₂S
Molecular Weight: 132.18

To a 5 mL microwave vial was added the radical inhibitor, *N*-phenyl-2-naphthylamine (30 mg, 0.13 mmol), the vial was sealed with a septum and cooled to -78 °C. SO₂ (1.50 mL, 35 mmol) was condensed slowly *via* needle into the vial under stirring, followed by piperylene (0.40 mL, 3.40 mmol). The resultant mixture was allowed to warm to room temperature and then stirred at this temperature for 24 h in the sealed vial. The vial was cooled again and slowly vented to leave a thick oil. Water (15 mL) was added and the product was extracted with DCM (3 x 15 mL), the combined organic layers were concentrated *in vacuo* and run through a short plug of silica, eluting with hexane:EtOAc (9:1) first, to remove the inhibitor, followed by DCM. The DCM fractions were concentrated to leave the pure sulfone as a slightly pale brown oil (165 mg, 85% (based on 59% *cis* + *trans* piperylene)).

¹H NMR (400 MHz, CDCl₃): δ 5.89 – 6.17 (m, 2H), 3.65 – 3.85 (m, 3H), 1.44 (d, *J* = 7.1 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 131.6, 122.7, 59.6, 55.0, 13.19 ppm.

3-(4-Methylpent-3-en-1-yl)-2,5-dihydrothiophene 1,1-dioxide **318**



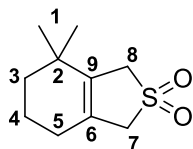
Chemical Formula: C₁₀H₁₆O₂S
Molecular Weight: 200.30

Myrcene (5.00 g, 36.7 mmol) was added to an open 10 mL microwave vial equipped with a stirrer. The vial was sealed and cooled to -78 °C, gaseous SO₂ (8.9 mL, 10 equiv.) was then condensed into the vial *via* a needle and the vial was resealed. The reaction was allowed to

warm to room temperature (3 bar internal vial pressure) and stirred for 20 h at r.t. after which time the septum was penetrated with a needle to allow evaporation of residual SO₂. The crude product was run through a short plug of silica (eluted with EtOAc) and concentrated *in vacuo* to give the product as a colourless liquid (5.13 g, 70%).

¹H NMR (400 MHz, CDCl₃) δ 5.72 – 5.67 (m, 1H, **7**), 5.12 – 5.03 (m, 1H, **3**), 3.81 (s, 2H, **9**), 3.69 (s, 2H, **8**), 2.26 – 2.13 (m, 4H, **4** + **5**), 1.71 (s, 3H, **1**), 1.62 (s, 3H, **1**) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 138.5 (**6**), 133.2 (**2**), 122.4 (**7**), 117.1 (**3**), 57.9, 57.0 (**8** + **9**), 33.1 (**4/5**), 25.7 (**1**), 25.5 (**4/5**), 17.8 (**1**) ppm; FT-IR ν_{\max} 779 (m), 910 (w), 1119 (s), 1233 (m), 1305 (s), 2921 (w); GC-MS R_t 2.57 min, m/z 136 [M-SO₂]⁺; ESI-HRMS m/z found [M+H]⁺ 201.0948, C₁₀H₁₇SO₂ requires 201.0949 (Δ = 0.5 ppm).

*4,4-Dimethyl-1,3,4,5,6,7-hexahydrobenzo[c]thiophene 2,2-dioxide*¹⁸² **319**



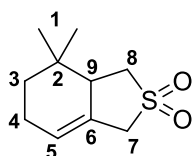
Chemical Formula: C₁₀H₁₆O₂S
Molecular Weight: 200.30

The sulfone **318** (200 mg, 1.0 mmol) was dissolved in toluene (5 mL) and H₂SO₄ (2 drops) was added. The reaction was stirred at room temperature for 24 h and the crude mixture was concentrated under reduced pressure. The residue was purified using SiO₂ column chromatography (7:3, hexane:EtOAc) to give a mixture of products (130 mg, 65% combined yield); **319**, 34%; **320**, 16%; **321**, 15% (**319** and **320** were inseparable), colourless crystalline solid, m.p. 85 - 88 °C (mixture of **319** and **320**).

¹H NMR (400 MHz, CDCl₃) δ 3.80 – 3.77 (m, 2H, **8**), 3.76 – 3.71 (m, 2H, **7**), 2.18 – 2.00 (m, 2H, **5**), 1.80 – 1.71 (m, 2H, **4**), 1.62 – 1.54 (m, 2H, **3**), 1.06 (s, 6H, **1**) ppm; ¹³C NMR (101

MHz, CDCl₃) δ 136.0 (**9**), 127.6 (**6**), 60.1 (**7**), 55.9 (**8**), 37.8 (**3**), 32.8 (**2**), 27.5 (**1**), 26.5 (**5**), 18.6 (**4**) ppm; FT-IR ν_{max} (**319** + **320**) 553 (s), 789 (m), 895 (w), 1023 (w), 1106 (m), 1134 (s), 1237 (m), 1254 (m), 1304 (s), 2919 (m); GC-MS R_t 2.38 min, m/z 136 [M-SO₂]⁺; ESI-HRMS m/z found [M+H]⁺ 201.0947, C₁₀H₁₇SO₂ requires 201.0949 (Δ = 1.0 ppm).

*4,4-Dimethyl-1,3,3a,4,5,6-hexahydrobenzo[c]thiophene 2,2-dioxide*¹⁸² **320**

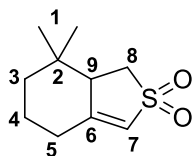


Chemical Formula: C₁₀H₁₆O₂S

Molecular Weight: 200.30

M.p. 85 - 88 °C (mixture of **319** and **320**). ¹H NMR (400 MHz, CDCl₃) δ 5.77 – 5.72 (m, 1H, **5**), 3.78 (obs, 2H, **7**), 3.25 – 3.20 (m, 1H, **8**), 2.92 – 2.85 (m, 2 x 1H, **8** + **9**), 2.19 – 2.12 (m, 2H, **4**), 1.54 – 1.47 (m, 2H, **3**), 1.03 (s, 3H, **1**), 0.88 (s, 3H, **1**) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 128.5 (**6**), 125.4 (**5**), 57.0 (**7**), 53.0 (**8**), 47.0 (**9**), 35.9 (**3**), 31.1 (**2**), 30.0 (**1**), 22.9 (**4**), 19.8 (**1**) ppm; FT-IR ν_{max} (**319** + **320**) 553 (s), 789 (m), 895 (w), 1023 (w), 1106 (m), 1134 (s), 1237 (m), 1254 (m), 1304 (s), 2919 (m); GC-MS R_t 2.38 min, m/z 136 [M-SO₂]⁺; ESI-HRMS m/z found [M+H]⁺ 201.0947, C₁₀H₁₇SO₂ requires 201.0949 (Δ = 1.0 ppm).

*7,7-Dimethyl-1,4,5,6,7,7a-hexahydrobenzo[c]thiophene 2,2-dioxide*¹⁸² **321**



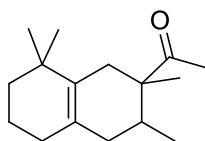
Chemical Formula: C₁₀H₁₆O₂S

Molecular Weight: 200.30

M.p. 69 - 72 °C. ¹H NMR (600 MHz, CDCl₃) δ 6.25 (t, J = 2.0 Hz, 1H, **7**), 3.26 (dd, J = 14.0, 9.2 Hz, 1H, **8**), 3.07 (dd, J = 14.0, 4.1 Hz, 1H, **8**), 2.77 – 2.80 (m, 1H, **9**), 2.68 – 2.52 (m, 1H, **5**), 2.12 – 2.02 (m, 1H, **5**), 1.81 – 1.74 (m, 1H, **4**), 1.67 – 1.54 (m, 2H, **4** + **3**), 1.49 – 1.40 (m,

¹H, **3**), 0.99 (s, 3H, **1**), 0.84 (s, 3H, **1**) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 155.4 (**6**), 124.1 (**7**), 50.7 (**8**), 50.2 (**9**), 39.4 (**3**), 36.1 (**2**), 30.2 (**1**), 29.4 (**5**), 21.6 (**4**), 19.1 (**1**) ppm; ; FT-IR ν_{\max} 554 (s), 638 (m), 806 (s), 837 (m), 817 (m), 1096 (s), 1138 (s), 1230 (m), 1280 (s), 1627 (w), 2870 (w), 2952 (w), 3071 (w); GC-MS R_t 4.98 min, m/z 201 [M+H]⁺; ASAP-HRMS m/z found [M+H]⁺ 201.0944, C₁₀H₁₇SO₂ requires 201.0949 (Δ = 2.5 ppm).

1-(2,3,8,8-tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalen-2-yl)ethanone (Iso E Super) 322

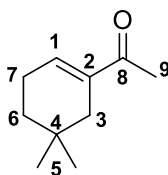


Chemical Formula: C₁₆H₂₆O
Molecular Weight: 234.38

Obtained as a mixture of 4 species. FT-IR ν_{\max} 732 (m), 1326 (m), 1382 (m), 1454 (m), 1630 (s), 1674 (m), 1681 (s), 1701 (m), 2963 (m); ASAP-HRMS m/z found [M+H]⁺ 235.2065, C₁₆H₂₇O requires 235.2062 (Δ = 1.3 ppm).

4.4. Galbascone

1-(5,5-Dimethylcyclohex-1-en-1-yl)ethanone (α) 65

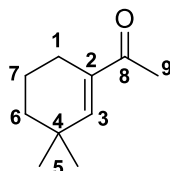


Chemical Formula: C₁₀H₁₆O
Molecular Weight: 152.23

¹H and ¹³C NMR spectra of α/β -mixture resolved by 2-D NMR experiments (COSY, HMBC, HSQC) and Pureshift ¹H NMR. ¹H NMR (700 MHz, CDCl₃) δ 6.87 (m, 1H, **1**), 2.28 (m(obsured), 2H, **7**), 2.28 (s, 3H, **9**), 2.01 (q, J = 2.2 Hz, 2H, **3**), 1.34 (t, J = 6.4 Hz, 2H, **6**), 0.90 (s, 6H, **5**) ppm; ¹³C NMR (176 MHz, CDCl₃) δ 199.5 (**8**), 139.7 (**1**), 138.7 (**2**), 36.4 (**3**),

34.2 (**6**), 28.5 (**4**), 28.0 (**5**), 25.3 (**9**), 24.1 (**7**) ppm; GC-MS R_t 3.32 min, m/z 152 $[M]^+$, 109 $[M-Ac]^+$; ASAP-HRMS m/z found $[M+H]^+$ 153.1281, $C_{10}H_{17}O$ requires 153.1279 ($\Delta = 1.3$ ppm).

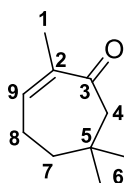
1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone (**β**) **66**



Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

1H and ^{13}C NMR spectra of α/β -mixture resolved by 2-D NMR experiments (COSY, HMBC, HSQC) and Pureshift 1H NMR. 1H NMR (700 MHz, $CDCl_3$) δ 6.53 (t, $J = 1.7$ Hz, 1H, **3**), 2.27 (s, 3H, **9**), 2.15 (td, $J = 6.3, 1.7$ Hz, 2H, **1**), 1.61 (m, 2H, **7**), 1.43 (m, 2H, **6**), 1.06 (s, 6H, **5**) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 199.9 (**8**), 149.7 (**3**), 137.3 (**2**), 36.3 (**6**), 32.7 (**4**), 29.1 (**5**), 25.2 (**9**), 23.1 (**1**), 19.1 (**7**) ppm; GC-MS R_t 3.24 min, m/z 152 $[M]^+$, 109 $[M-Ac]^+$; ASAP-HRMS m/z found $[M+H]^+$ 153.1281, $C_{10}H_{17}O$ requires 153.1279 ($\Delta = 1.3$ ppm).

2,6,6-Trimethylcyclohept-2-enone (Dihydroeucarvone)¹²² **216**

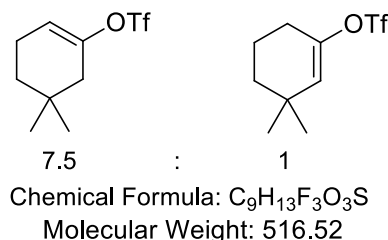


Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

1H and ^{13}C NMR spectra resolved from a mixture of α/β -isomers and dihydroeucarvone by 2-D NMR experiments (COSY, HMBC, HSQC) and Pureshift 1H NMR. 1H NMR (700 MHz, $CDCl_3$) δ 6.60 (m, 1H, **9**), 2.42 (s, 2H, **4**), 2.30 (m, 2H, **8**), 1.77 (m, 3H, **1**), 1.51 (m, 2H, **7**), 1.00 (s, 6H, **6**) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) δ 203.1 (**3**), 144.7 (**9**), 139.1 (**2**), 56.3 (**4**),

42.0 (7), 32.7 (5), 29.3 (6), 25.9 (8), 18.9 (1) ppm; GC-MS R_t 3.27 min, m/z 152 $[M]^+$, 109 $[M-Ac]^+$; ASAP-HRMS m/z found $[M+H]^+$ 153.1281, $C_{10}H_{17}O$ requires 153.1279 ($\Delta = 1.3$ ppm).

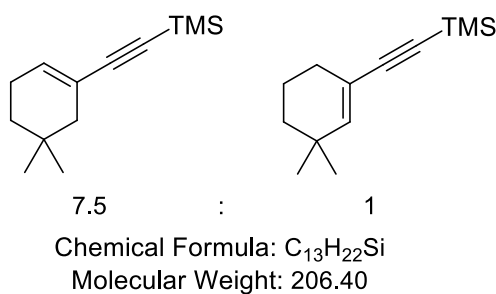
*5,5-Dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate*¹⁸³ **217/218**



LDA was prepared by adding *n*-BuLi (2.4 M, 2.80 mL, 6.75 mmol) to a solution of diisopropylamine (0.96 mL, 6.75 mmol) in dry THF (25 mL) at 0 °C under an N_2 atmosphere. The reaction was stirred at this temperature for 30 min, then lowered to -78 °C and 3,3-dimethylcyclohexanone (90%), (630 mg, 5.0 mmol) was added. This was left to stir for a further 30 min and then *N*-phenyl-bis(trifluoromethanesulfonimide) (2.50 g, 7.0 mmol) was added. The reaction was stirred at -78 °C for a further 10 min and then allowed to warm to room temperature and stirred for 16 h. The solvent was removed *in vacuo* and the residue was diluted with Et_2O (20 mL) and extracted from saturated aqueous $NaHCO_3$ (20 mL) with further Et_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated to leave the crude product. This was purified using SiO_2 column chromatography (97:3, hexanes: $EtOAc$) to afford the product as a colourless liquid (1.14 g, 88%), (7.5:1 mixture of isomers).

Major isomer: 1H NMR (400 MHz, $CDCl_3$) δ 5.76 (m, 1H, C=CH), 2.20 (s, 2H, CH_2), 2.12 (m, 2H, CH_2), 1.38 (t, $J = 6.3$ Hz, 2H, CH_2), 1.02 (s, 6H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 120.1, 117.1, 41.0, 33.9, 31.1, 27.8, 21.7; FT-IR ν_{max} 610 (s), 863 (m), 1039 (m), 1140 (s), 1201 (s), 1414 (m), 2930 (w) cm^{-1} ; GC-MS R_t 3.10 min, m/z 258 $[M]^+$, 125 $[M-Tf]^+$.

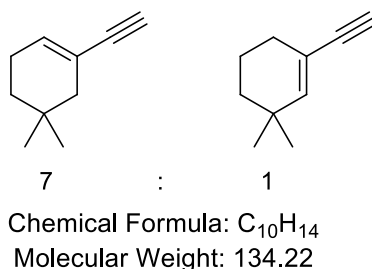
((5,5-Dimethylcyclohex-1-en-1-yl)ethynyl)trimethylsilane **220/221**



The vinyl triflates **217/218** (500 mg, 1.90 mmol), Pd(PPh₃)₂Cl₂ (35 mg, 0.05 mmol), copper(I) iodide (20 mg, 0.1 mmol) and diisopropylamide (0.80 mL, 5.7 mmol) were taken up in dry THF (15 mL) and stirred at 0 °C. Trimethylsilylacetylene (0.33 mL, 2.3 mmol) was added and the mixture was allowed to warm to room temperature, it was then stirred for 1 h. After this time the reaction mixture was partitioned between Et₂O (15 mL) and 1 M HCl (20 mL) and extracted with Et₂O (2 x 15 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. The material was passed through a short plug of silica (hexanes:Et₂O, 10:1) and the solvent removed *in vacuo*. Purification by SiO₂ column chromatography (9:1, hexanes:EtOAc) afforded the product as a colourless liquid (362 mg, 92%), (7.5:1 mixture of isomers).

Major isomer: ¹H NMR (400 MHz, CDCl₃) δ 6.17 (m, 1H, C=CH), 2.20 – 2.06 (m, 2H, CH₂), 1.94 (q, *J* = 2.3 Hz, 2H, CH₂), 1.33 (t, *J* = 6.4 Hz, 2H, CH₂), 0.94 (s, 6H, CH₃), 0.20 (s, 9H, Si(CH₃)₃); ¹³C NMR (101 MHz, CDCl₃) δ 134.8, 119.7, 107.4, 90.5, 42.6, 34.1, 28.8, 28.0, 23.6, 0.1; FT-IR ν_{max} 647 (m), 758 (m), 836 (s), 1249 (m), 2069 (w), 2144 (w), 2956 (w) cm⁻¹; GC-MS R_t 3.67 min, *m/z* 206 [M]⁺, 191 [M-Me]⁺; ASAP-HRMS *m/z* found [M]⁺ 206.1490, C₁₃H₂₂Si requires 206.1491 (Δ = 0.5 ppm).

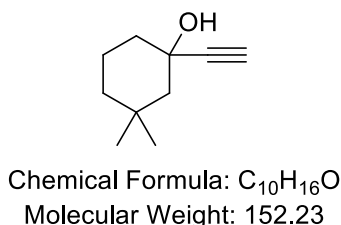
1-Ethynyl-5,5-dimethylcyclohex-1-ene **222/223**



The TMS-acetylenes **220/221** (53 mg, 0.26 mmol) were dissolved in MeOH (3 mL) and K₂CO₃ (100 mg, 0.75 mmol, 3 equiv.) was added and the mixture stirred for 6 h at room temperature. After this time the reaction was partitioned between hexane (10 mL) and H₂O (5 mL) and the product was extracted with more hexane (10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo* to leave the product as a colourless liquid (25 mg, 72%), (7:1 mixture of isomers).

Major isomer: ¹H NMR (600 MHz, CDCl₃) δ 6.16 (m, 1H, C=CH), 2.76 (s, 1H, C≡CH), 2.13 – 2.08 (m, 2H, CH₂), 1.91 (q, *J* = 2.3 Hz, 2H, CH₂), 1.31 (t, *J* = 6.4 Hz, 2H, CH₂), 0.91 (s, 6H, CH₃); ¹³C NMR (151 MHz, CDCl₃) δ 135.1, 118.7, 85.8, 74.0, 42.5, 34.1, 28.7, 27.9, 23.5; FT-IR ν_{max} 600 (s), 636 (s), 807 (s), 848 (m), 1210 (s), 1700 (m), 2096 (w), 2922 (s), 3315 (m) cm⁻¹; GC-MS R_t 2.67 min, *m/z* 134 [M]⁺, 119 [M-Me]⁺.

*1-Ethynyl-3,3-dimethylcyclohexanol*¹⁸⁴ **59**

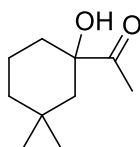


3,3-Dimethylcyclohexanone **58**, (1.26 g, 10.0 mmol) was dissolved in dry THF (10 mL) and cooled to -10 °C with stirring under an N₂ atmosphere. Ethynylmagnesium bromide (0.5 M in

THF, 24 mL, 1.2 equiv.) was added and the reaction was stirred for 10 min at -10 °C. The reaction was allowed to warm to r.t. and stirred for a further 2 h. The reaction was then quenched with saturated aqueous NH₄Cl solution (20 mL) and concentrated under reduced pressure. The product was extracted with Et₂O (2 x 30 mL) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the product as a colourless liquid with a woody odour (1.43 g, 94%).

¹H NMR (700 MHz, CDCl₃) δ 2.45 (s, 1H), 1.86 (m, 2H), 1.75 – 1.48 (m, 4H), 1.31 – 1.20 (m, 2H), 1.02 (s, 3H), 0.98 (s, 3H) ppm; ¹³C NMR (176 MHz, CDCl₃) δ 89.2, 71.4, 67.6, 50.9, 39.9, 38.6, 31.3, 28.5, 22.5, 19.2 ppm; FT-IR ν_{max} 624 (s), 963 (m), 1020 (s), 1063 (m), 1192 (m), 1365 (m), 1457 (m), 1704 (w), 2948 (m), 3310, (m), 3400 (w, br); GC-MS R_t 2.95 min, *m/z* 152 [M]⁺; ASAP-HRMS *m/z* found [M+H]⁺ 153.1285, C₁₀H₁₇O requires 153.1279 (Δ = 3.9 ppm).

1-(1-Hydroxy-3,3-dimethylcyclohexyl)ethanone **224**



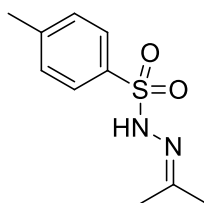
Chemical Formula: C₁₀H₁₈O₂
Molecular Weight: 170.25

The propargylic alcohol **59** (0.500 g, 3.30 mmol) was dissolved in MeOH (15 mL) and stirred at r.t. Mercury(II) acetate (0.105 g, 10 mol%) was added along with H₂SO₄ (1 drop) and the mixture was stirred under reflux for 1 h. After which time the MeOH was removed under reduced pressure and 1 M HCl (15 mL) was added to the residue. The resultant mixture was stirred at r.t. for 1 h and the product extracted using DCM (3 x 20 mL). The combined DCM layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the

crude product. Pure product was obtained by SiO₂ column chromatography (8:2, hexane:EtOAc) as a yellow liquid (0.390 g, 70%).

R_f (8:2, hexane:EtOAc) 0.3. ¹H NMR (400 MHz, CDCl₃) δ 3.61 (s, 1H), 2.26 (s, 3H), 1.99 – 1.81 (m, 1H), 1.70 – 1.44 (m, 5H), 1.35 – 1.19 (m, 2H), 1.14 (s, 3H), 0.95 (s, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 212.9, 79.3, 44.7, 38.9, 34.4, 34.0, 30.4, 26.5, 23.7, 18.0 ppm; FT-IR ν_{max} 620 (m), 955 (m), 988 (m), 1033 (m), 1067 (m), 1155 (s), 1229 (m), 1365 (m), 1455 (m), 1699 (s), 2949 (m), 3468 (w, br); GC-MS R_t 3.32 min, *m/z* 171 [M+H]⁺, 127 [M-Ac]⁺.

*4-Methyl-N'-(propan-2-ylidene)benzenesulfonohydrazide*¹⁸⁵ **225**



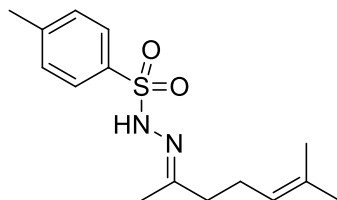
Chemical Formula: C₁₀H₁₄N₂O₂S
Molecular Weight: 226.30

p-Toluenesulfonyl hydrazine (5.58g, 30.0 mmol) was taken up in THF (20 mL) and acetone (2.7 mL, 1.2 equiv.) was added. After stirring at room temperature for 1 h, the reaction was quenched with aqueous saturated NaHCO₃ (30 mL) and the product was extracted with CH₂Cl₂ (3 x 40 mL). After drying over Na₂SO₄ and removal of the solvent under reduced pressure, a pale yellow solid remained which was triturated with sonication using MeOH, giving the title compound as a pale yellow solid (5.94 g, 88%), (mp 149-150.5 °C).

¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 2.43 (s, 3H), 1.92 (s, 3H), 1.81 (s, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 156.6, 143.9, 135.5, 129.5, 128.0, 25.3, 21.6, 17.1 ppm; FT-IR ν_{max} 533 (m), 559 (s), 582 (s), 668 (s), 810 (m), 993 (m),

1086 (m), 1158 (s), 1330 (m), 2366 (w), 3225 (m); GC-MS R_t 5.24 min, m/z 226 $[M]^+$, 71 $[M-Ts]^+$.

4-Methyl-N'-(6-methylhept-5-en-2-ylidene)benzenesulfonohydrazide **227**

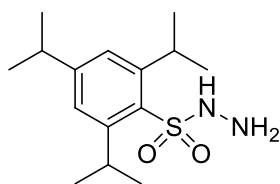


Chemical Formula: $C_{15}H_{22}N_2O_2S$
Molecular Weight: 294.41

Tosyl hydrazone **225** (3.00 g, 13.3 mmol) was dissolved in dry THF (35 mL) and cooled to -78 °C. n-Butyl lithium (2.4 M in hexane, 11.9 mL, 2.2 equiv.) was added slowly and the reaction was stirred at -78 °C for 20 min. To the reaction was added dropwise 1-bromo-3-methylbut-2-ene (1.86 mL, 1.2 equiv.) and the resultant mixture was stirred at -78 °C for 20 min and then allowed to warm to 0 °C over the period of 1 h. The reaction was then quenched with aqueous 1 M HCl (20 mL) and the product was extracted with EtOAc (3 x 30 mL), washed with brine (80 mL) and dried over Na_2SO_4 to give, after removal of the solvent *in vacuo*, the crude product. This was purified using SiO_2 column chromatography (8:2 – 1:1, hexane:EtOAc), giving the pure product as a pale yellow solid (3.34 g, 85%).

1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 5.14 – 4.90 (m, 1H), 2.44 (s, 3H), 2.30 – 2.11 (m, 4H), 1.78 (s, 3H), 1.62 (s, 3H), 1.56 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 143.9, 135.4, 132.4, 129.4, 128.1, 122.8, 38.7, 25.6, 24.6, 21.6, 17.6, 15.7 ppm; FT-IR ν_{max} 547 (s, br), 664 (s), 814 (m), 929 (m), 1068 (m), 1166 (s), 1318 (m); GC-MS R_t 6.27 min, m/z 294 $[M]^+$, 139 $[M-Ts]^+$; HRMS m/z found $[M+H]^+$ 295.1478, $C_{15}H_{23}N_2O_2S$ requires 295.1480 (Δ = 0.7 ppm).

2,4,6-Triisopropylbenzenesulfonohydrazide¹⁸⁶ **323**

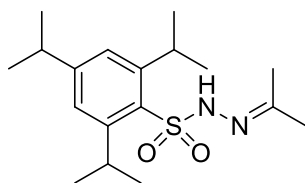


Chemical Formula: C₁₅H₂₆N₂O₂S
Molecular Weight: 298.44

Triisopropylbenzenesulfonyl chloride (3.03 g, 10.0 mmol) was dissolved in THF (15 mL) and stirred at -10 °C. Hydrazine (1 M solution in THF), (15 mL, 1.5 equiv) was added and the reaction was stirred for 20 h and gradually brought to r.t. H₂O (30 mL) was added to dissolve precipitates and the product was extracted using Et₂O (3 x 30 mL). The combined organic layers were washed with brine (2 x 30 mL), dried over Na₂SO₄, filtered through a short plug of celite and concentrated under reduced pressure. The resultant solid was washed with petroleum ether and filtered to give the product as a yellow solid (2.17 g, 73%).

¹H NMR (400 MHz, CDCl₃) δ 7.22 (s, 2H), 5.53 (br s, 1H), 4.17 (p, *J* = 6.7 Hz, 2H), 3.60 (br s, 2H), 2.94 (p, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 6.8 Hz, 12H), 1.29 (d, *J* = 7.0, 5.0 Hz, 6H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 153.8, 151.8, 128.6, 124.0, 34.2, 29.8, 24.9, 23.5 ppm; FT-IR ν_{max} 555 (m), 652 (m), 884 (m), 1150 (s), 1321 (m), 1426 (m), 1601, (m), 2957 (m), 3200 (w, br); GC-MS R_t 3.66 min, *m/z* 204 [M-SO₂NHNH₂]⁺.

2,4,6-Triisopropyl-*N'*-(propan-2-ylidene)benzenesulfonohydrazide¹⁸⁶ **229**



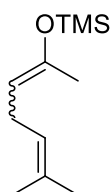
Chemical Formula: C₁₈H₃₀N₂O₂S

Molecular Weight: 338.51

Hydrazine **323** (1.49 g, 5.00 mmol) was stirred at room temperature in THF (5 mL) and acetone (1.0 mL, 1.2 equiv.) was added. The mixture was stirred at r.t. in a closed vessel for 6 h and then concentrated *in vacuo* to give the product as a white solid (1.62 g, 96%).

¹H NMR (400 MHz, CDCl₃) δ 7.28 (br, s, 1H), 7.19 (s, 2H), 4.28 (p, *J* = 6.8, Hz, 2H), 2.93 (p, *J* = 6.9 Hz, 1H), 1.94 (s, 3H), 1.81 (s, 3H), 1.29 (d, *J* = 6.8 Hz, 12H), 1.27 (d, *J* = 7.8 Hz, 6 H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 153.9, 153.1, 151.3, 131.4, 123.8, 34.1, 29.9, 25.4, 24.8, 23.6, 16.4 ppm; FT-IR *v*_{max} 561 (s), 580 (s), 663 (s), 809 (m), 881 (m), 1170 (s), 1327 (m), 1384 (m), 1426 (m), 1599 (w), 2959 (m), 3244 (m); GC-MS *R*_t 5.75 min, *m/z* 339 [M]⁺, 282 [M-NC(CH₃)₂]⁺, 267 [M-NHNC(CH₃)₂]⁺.

Trimethyl((6-methylhepta-2,5-dien-2-yl)oxy)silane¹⁸⁷ **232/233**



Chemical Formula: C₁₁H₂₂OSi

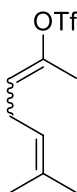
Molecular Weight: 198.38

To a stirred mixture of 6-methyl-5-hepten-2-one (12.6 g, 100 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (17.9 mL, 1.2 equiv.) in CH₂Cl₂ (80 mL) at 40 °C was added chlorotrimethylsilane (14.0 mL, 1.1 equiv.). After 4 h of stirring at 40 °C, the mixture was diluted with hexane (30 mL) and washed with 1 M HCl (2 x 50 mL) followed by saturated

NaHCO₃ (2 x 50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to leave a clear liquid which contained traces of starting material and the product isomers in a 1:1 ratio (18.5 g, 93%).

Purification by SiO₂ column chromatography (95:5, hexane:EtOAc) afforded a ~1.8:1 mixture of *E:Z* product isomers which was used for characterisation. R_f (9:1, hexane:EtOAc) 0.7. ¹H NMR (400 MHz, CDCl₃) **Isomer A**: δ 5.10 (m, 1H), 4.43 (t, *J* = 7.1 Hz, 1H), 2.69 (m, 2H), 1.79 (s, 3H), 1.70 (s, 3H), 0.23 (s, 9H) ppm; **Isomer B**: δ 5.10 (m, 1H), 4.07 (m, 2H), 2.20 – 2.02 (m, 4H), 1.70 (s, 3H), 1.65 (s, 3H), 0.22 (s, 9H) ppm; FT-IR ν_{max} 751 (m), 840 (s), 1001 (m), 1153 (w), 1252 (m), 1332 (w), 2916 (w); GC-MS R_t 3.06 + 3.14 min, *m/z* 198 [M]⁺, 183 [M-Me]⁺, 130 [HC=C(OTMS)CH₃]⁺.

6-Methylhepta-2,5-dien-2-yl trifluoromethanesulfonate 234/235



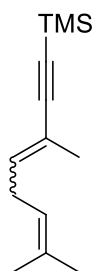
Chemical Formula: C₉H₁₃F₃O₃S
Molecular Weight: 258.26

TMS enol **232/233** (1.00 g, 5.00 mmol) was dissolved in dry dimethoxyethane (10 mL) and cooled to -78 °C with stirring under an N₂ atmosphere. Methyl lithium (1.6 M in Et₂O), (3.4 mL, 1.1 equiv.) was added and the mixture was stirred for 20 min at -78 °C and then allowed to warm to 0 °C at which point it was stirred for a further 20 min. The reaction was cooled to -78 °C and *N*-phenyl-bis(trifluoromethanesulfonimide) (1.79 g, 1.1 equiv.) was added as a solution in dry dimethoxyethane (10 mL), the mixture was then allowed to slowly warm to room temperature and stirred for 2 h. Dilute aqueous NaHCO₃ solution (15 mL) was added and the product was extracted using Et₂O (2 x 20 mL), the combined organic layers were

concentrated *in vacuo* and the residue was purified by SiO₂ column chromatography (95:5, hexane:EtOAc) to give a mixture of product isomers as a colourless liquid (0.620 g, 48%).

Single isomer obtained by further SiO₂ column chromatography for characterisation. R_f (9:1, hexane:EtOAc) 0.6. ¹H NMR (700 MHz, CDCl₃) δ 5.17 (td, *J* = 7.4, 1.1 Hz, 1H), 5.05 (m, 1H), 2.83 (t, *J* = 7.0 Hz, 2H), 2.04 (d, *J* = 1.3 Hz, 3H), 1.69 (d, *J* = 1.4 Hz, 3H), 1.62 (s, 3H) ppm; ¹³C NMR (176 MHz, CDCl₃) δ 144.6, 134.0, 120.8, 119.8, 117.4, 25.6, 24.9, 19.6, 17.6 ppm; FT-IR ν_{max} 581 (m), 634 (m), 895 (m), 929 (m), 1142 (s), 1203 (s), 1413 (m); GC-MS R_t 3.03 min, *m/z* 258 [M]⁺, 125 [M-Tf]⁺; ASAP-HRMS *m/z* found [M+H]⁺ 259.0618, C₉H₁₄O₃F₃S requires 259.0616 (Δ = 0.8 ppm).

(3,7-Dimethylocta-3,6-dien-1-yn-1-yl)trimethylsilane **236**



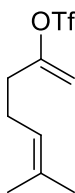
Chemical Formula: C₁₃H₂₂Si
Molecular Weight: 206.40

Enol triflate **234/235** (mixture of *endo* isomers), (0.500 g, 1.90 mmol), Pd(PPh₃)₂Cl₂ (35 mg, 0.05 mmol), copper(I) iodide (20 mg, 0.1 mmol) and diisopropylamide (0.80 mL, 5.7 mmol) were taken up in dry THF (15 mL) and stirred at 0 °C. Trimethylsilylacetylene (0.33 mL, 2.3 mmol) was added and the mixture was allowed to warm to room temperature, it was then stirred for 1 h. After this time the reaction mixture was partitioned between Et₂O (20 mL) and 1 M HCl (20 mL) and extracted with Et₂O (2 x 20 mL). The combined organic layers were washed with brine (50 mL) and dried over Na₂SO₄, then after filtration passed through a short plug of

silica (hexanes:Et₂O, 10:1) and solvent was removed *in vacuo*, the crude product was obtained as a colourless liquid (389 mg, 99%).

One *endo*-isomer's ¹H NMR spectrum resolved from a mixture of three isomers. R_f (9:1, hexane:EtOAc) 0.8 ¹H NMR (400 MHz, CDCl₃) δ 5.66 (td, *J* = 7.5, 1.5 Hz, 1H), 5.14 (m, 1H), 2.98 (t, *J* = 7.6 Hz, 2H), 1.85 (s, 3H), 1.72 (s, 3H), 1.69 (s, 3H), 0.22 (s, 9H) ppm; FT-IR ν_{max} 647 (m), 759 (m), 838 (s), 1145 (w), 1210 (m), 1249 (m); GC-MS R_t 3.43, 3.46 and 3.70 min, *m/z* 206 [M]⁺, 191 [M-Me]⁺; ASAP-HRMS *m/z* found [M+H]⁺ 207.1563, C₁₃H₂₃Si requires 207.1569 (Δ = 2.9 ppm).

*6-Methylhepta-1,5-dien-2-yl trifluoromethanesulfonate*¹⁸⁸ **237**

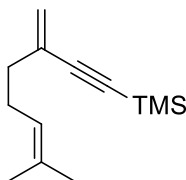


Chemical Formula: C₉H₁₃F₃O₃S
Molecular Weight: 258.26

A solution of LDA was prepared by adding *n*-BuLi (2.4 M, 2.29 mL, 5.5 mmol) to a solution of diisopropylamine (0.78 mL, 5.5 mmol) in dry THF (25 mL) at 0 °C under an N₂ atmosphere and stirred for 30 min. The solution was then cooled to -78 °C and 6-methyl-5-hepten-2-one (631 mg, 5.0 mmol) was added. The mixture was left to stirred for 30 min and then *N*-phenyl-bis(trifluoromethanesulfonimide) (1.79 g, 5.0 mmol) was added, this was left to stir at -78 °C for a further 10 min and then removed from the acetone/dry ice bath and stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was diluted with Et₂O (25 mL) and extracted against aqueous NaHCO₃ (20 mL). The combined organic layers were dried over Na₂SO₄, filtered and then concentrated to leave the crude product. This was purified using SiO₂ column chromatography (95:5, hexanes:EtOAc) to afford the product as a clear liquid (710 mg, 55%).

^1H NMR (400 MHz, CDCl_3) δ 5.15 – 5.06 (m, 2H, $\text{C}=\text{CH}_2$), 4.96 (dt, $J = 3.6, 1.1$ Hz, 1H, $\text{C}=\text{CH}$), 2.42 – 2.35 (m, 2H, CH_2), 2.30 – 2.21 (m, 2H, CH_2), 1.72 (d, app, $J = 1.3$ Hz, 3H, CH_3), 1.66 (s, 3H, CH_3); ^{13}C NMR (101 MHz, CDCl_3) δ 156.6, 133.7, 121.5, 119.8, 104.3, 34.0, 25.6, 24.6, 17.7; FT-IR ν_{max} 602 (m), 890 (m), 930 (m), 1143 (s), 1203 (s), 1416 (m) cm^{-1} ; GC-MS R_t 3.03 min, m/z 258 $[\text{M}]^+$, 125 $[\text{M-Tf}]^+$; ASAP-HRMS m/z found $[\text{M+H}]^+$ 259.0619, $\text{C}_9\text{H}_{14}\text{F}_3\text{O}_3\text{S}$ requires 259.0616 ($\Delta = 1.2$ ppm).

*Trimethyl(7-methyl-3-methyleneoct-6-en-1-yn-1-yl)silane*¹⁸⁸ **238**



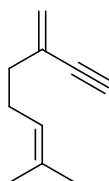
Chemical Formula: $\text{C}_{13}\text{H}_{22}\text{Si}$
Molecular Weight: 206.40

The vinyl triflate **237** (500 mg, 1.90 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (35 mg, 0.05 mmol), copper(I) iodide (20 mg, 0.1 mmol) and diisopropylamide (0.80 mL, 5.7 mmol) were taken up in dry THF (15 mL) and stirred at 0 °C. Trimethylsilylacetylene (0.33 mL, 2.3 mmol) was added and the mixture was allowed to warm to room temperature, it was then stirred for 1 h. After this time the reaction mixture was partitioned between Et_2O (30 mL) and 1M HCl (20 mL) and extracted with Et_2O (2 x 30 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4 , then after filtration passed through a short plug of silica (hexane: Et_2O , 10:1), solvent was removed *in vacuo* and the product was obtained as a brown liquid (390 mg, 99%).

^1H NMR (400 MHz, CDCl_3) δ 5.39 (m, 1H, $\text{C}=\text{CH}$), 5.28 – 5.23 (m, 1H, $\text{C}=\text{CH}$), 5.13 (m, 1H, $\text{C}=\text{CH}$), 2.29 – 2.14 (m, 4H, $\text{H}_2\text{C}-\text{CH}_2$), 1.71 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 0.21 (s, 9H,

Si(CH₃)₃; ¹³C NMR (101 MHz, CDCl₃) δ 132.2, 131.5, 123.4, 121.9, 105.6, 93.9, 37.3, 26.7, 25.7, 17.7, -0.02; FT-IR ν_{\max} 759 (m), 838 (s), 1250 (m), 2069 (w), 2114 (w), 2965 (w) cm⁻¹; GC-MS R_t 3.48 min, m/z 206 [M]⁺, 133 [M-TMS]⁺; ASAP-HRMS m/z found [M+H]⁺ 207.1561, C₁₃H₂₃Si requires 207.1569 (Δ = 3.9 ppm).

*7-Methyl-3-methyleneoct-6-en-1-yne*¹⁸⁸ **62**



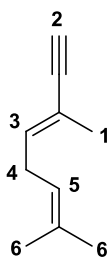
Chemical Formula: C₁₀H₁₄

Molecular Weight: 134.22

The TMS-acetylene **238** (75 mg, 0.36 mmol) was dissolved in MeOH (3 mL) and K₂CO₃ (150 mg, 1.08 mmol, 3 equiv.) was added, the mixture was stirred at room temperature for 6 h. After this time the reaction was partitioned between hexane (10 mL) and H₂O (10 mL) and the product was extracted with more hexane (10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo* to leave the product as a pale brown liquid (40 mg, 83%).

¹H NMR (400 MHz, CDCl₃) δ 5.44 (s, 1H, C=CH₂), 5.32 (s, 1H, C=CH₂), 5.12 (m, 1H, C=CH), 2.91 (s, 1H, C≡CH), 2.30 – 2.16 (m, 4H, H₂C-CH₂), 1.71 (s, 3H, CH₃), 1.65 (s, 3H, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ 132.4, 130.5, 123.1, 122.8, 84.1, 73.5, 37.1, 26.6, 25.7, 17.7; FT-IR ν_{\max} 957 (w), 1073 (w), 1151 (w), 1230 (w), 1383 (w), 2982 (s), 3660 (w) cm⁻¹; GC-MS R_t 2.57 min, m/z 134 [M]⁺, 119 [M-Me]⁺.

(E)-3,7-Dimethylocta-3,6-dien-1-yne **64**



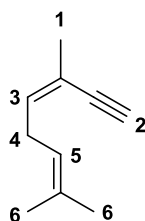
Chemical Formula: C₁₀H₁₄

Molecular Weight: 134.22

Tentative ¹H-NMR assignment of isomers based on reactivity differences:

¹H NMR (700 MHz, CDCl₃) δ 5.68 (t, *J* = 7.4 Hz, 1H, **3**), 5.08 (m, 1H, **5**), 3.10 (s, 1H, **2**), 2.95 (t, *J* = 7.5 Hz, 2H, **4**), 1.69 (s, 3H, **6**), 1.69 (s, 3H, **1**), 1.65 (s, 3H, **6**) ppm.

(Z)-3,7-Dimethylocta-3,6-dien-1-yne **63**

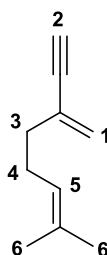


Chemical Formula: C₁₀H₁₄

Molecular Weight: 134.22

¹H NMR (700 MHz, CDCl₃) δ 5.90 (t, *J* = 7.5 Hz, 1H, **3**), 5.10 (m, 1H, **5**), 2.77 (t, *J* = 7.5 Hz, 2H, **4**), 2.75 (s, 1H, **2**), 1.85 (s 3H, **6**), 1.81 (s, 3H, **6**), 1.69 (s, 3H, **1**) ppm.

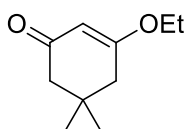
7-Methyl-3-methyleneoct-6-en-1-yne **62**



Chemical Formula: C₁₀H₁₄
Molecular Weight: 134.22

¹H NMR (700 MHz, CDCl₃) δ 5.42 (s, 1H, **1**), 5.29 (s, 1H, **1**), 5.10 (m, 1H, **5**), 2.88 (s, 1H, **2**), 2.25 – 2.15 (m, 4H, **3 + 4**), 1.69 (m, 3H, **6**), 1.62 (s, 3H, **6**) ppm.

*3-Ethoxy-5,5-dimethylcyclohex-2-enone*¹⁸⁹ **253**



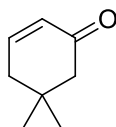
Chemical Formula: C₁₀H₁₆O₂
Molecular Weight: 168.23

Dimedone (14.0 g, 0.10 mol) was dissolved in toluene (150 mL) and EtOH (50 mL) and *p*-TSA (0.95 g, 5 mmol, 5 mol%) was added. This was stirred under reflux in a round-bottomed flask equipped with a Dean-Stark trap. After 18 h the reaction mixture was allowed to cool to r.t. and was concentrated *in vacuo*. EtOAc (200 mL) and 1 M aqueous NaOH were added along with H₂O (200 mL) and the product was extracted with further EtOAc (3 x 100 mL). The combined organic layers were dried over Na₂SO₄ and filtered and the solvent was removed *in vacuo* to leave the product as a slightly off-white solid (15.5 g, 93%), m.p. 59-60 °C (*i*PrOH), (lit. 59-60 °C).¹⁹⁰

¹H NMR (400 MHz, CDCl₃) δ 5.31 (s, 1H), 3.87 (q, *J* = 7.0 Hz, 2H), 2.24 (s, 2H), 2.17 (s, 2H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.04 (s, 6H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 199.5, 176.1, 101.4, 64.2, 50.7, 42.9, 32.4, 28.2, 14.1 ppm; FT-IR *v*_{max} 634 (m), 870 (m), 1032 (m), 1145 (s), 1291

(s), 1360 (m), 1376 (m), 1470 (m), 1600 (s), 1647 (m), 2956 (w); GC-MS R_t 3.79 min, m/z 168 $[M]^+$, 139 $[M-Et]^+$, 124 $[M-OMe]^+$

5,5-Dimethylcyclohex-2-enone¹⁹¹ **57**

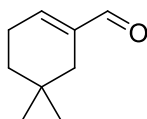


Chemical Formula: C₈H₁₂O
Molecular Weight: 124.18

To a stirred mixture of lithium aluminium hydride (660 mg, 17.4 mmol, 0.4 equiv.) in dry Et₂O (100 mL) at 0 °C was added a solution of the enol-ether **253** (7.82 g, 43.4 mmol) in dry Et₂O (20 mL) dropwise *via* syringe. This was left to stir for 18 h while allowing to warm to r.t., the mixture was again cooled to 0 °C and aqueous 10% H₂SO₄ (30 mL) was added dropwise. This was then allowed to warm to r.t. and stirred for a further 1 h before the ether layer was separated and the aqueous layer was extracted with Et₂O (2 x 50 mL), the combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and the ether was removed *in vacuo* leaving the product as a very pale yellow liquid (5.32 g, 98%).

¹H NMR (400 MHz, CDCl₃) δ 6.86 (dtd, J = 9.8, 4.1, 1.4 Hz, 1H), 6.02 (dd, J = 10.1, 2.1 Hz, 1H), 2.27 (s, 2H), 2.24 (dt, J = 3.8, 1.8 Hz, 2H), 1.04 (d, J = 0.7 Hz, 6H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 199.9, 148.4, 128.9, 51.7, 39.9, 33.9, 28.3 ppm; FT-IR ν_{max} 500 (w), 732 (m), 902 (m), 1162 (w), 1243 (w), 1389 (m), 1674 (s), 2958 (w); GC-MS R_t 2.72 min, m/z 124 $[M]^+$.

5,5-dimethylcyclohex-1-enecarbaldehyde **259**



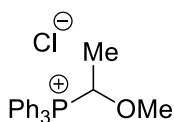
Chemical Formula: C₉H₁₄O

Molecular Weight: 138.21

(Methoxymethyl)triphenylphosphonium chloride (5.14 g, 15.0 mmol, 1.5 equiv.) was stirred in dry THF (20 mL) at -78 °C under N₂. *n*-BuLi (2.5 M in hexane), (6.0 mL, 15 mmol, 1.5 equiv.) was added dropwise *via* syringe to give a deep red solution, this was allowed to warm to 0 °C over 10 min before being re-cooled to -78 °C. A solution of 5,5-dimethylcyclohex-2-enone **57** (1.24 g, 10.0 mmol, 1 equiv.) in dry THF (5 mL) was then added dropwise *via* syringe at -78 °C and the resultant mixture was stirred and allowed to reach r.t. overnight. HCl (2 M in Et₂O), (15.0 mL, 30.0 mmol, 3 equiv.) was added and this was stirred for 1 h at r.t. and the crude product was concentrated *in vacuo*. EtOAc (30 mL) and H₂O (20 mL) were added and the product was extracted with more EtOAc (30 mL). The organic layers were combined, dried over Na₂SO₄ and filtered and then concentrated *in vacuo*. The crude product was purified by SiO₂ column chromatography, (9:1, hexane:EtOAc) to give the pure product as a colourless liquid (350 mg, 25%), R_f (9:1, hexane:EtOAc) 0.3.

¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H), 6.81 (m, 1H), 2.39 (m, 2H), 2.02 (q, *J* = 2.2 Hz, 2H), 1.45 (t, *J* = 6.4 Hz, 2H), 0.95 (s, 6H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 194.5, 150.3, 140.8, 34.8, 34.8, 28.3, 27.9, 24.5 ppm; FT-IR ν_{max} 678 (m), 1138 (m), 1212 (m), 1365 (w), 1641 (m), 1861 (s), 2953 (m); GC-MS R_t 3.04 min, *m/z* 138 [M]⁺, 109 [M-CHO]⁺; ASAP-HRMS *m/z* found [M+H]⁺ 139.1124, C₉H₁₅O requires 139.1123 (Δ = 0.7 ppm).

*(1-Methoxyethyl)triphenylphosphonium chloride*¹²⁵ **262**



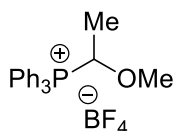
Chemical Formula: C₂₁H₂₂ClOP

Molecular Weight: 356.83

Acetyl chloride (3.6 mL, 50 mmol, 1 equiv.) was added dropwise to a neat mixture of 1,1-dimethoxyethane (4.51 g, 50 mmol, 1 equiv.) and zinc(II) chloride (6 mg, 0.05 mmol 0.1 mol%) under N₂ at r.t. and the resultant mixture was stirred for 30 min at r.t. This was then transferred to a stirred solution of triphenylphosphine (13.11 g, 50 mmol, 1 equiv.) in dry Et₂O (100 mL) and stirred for 16 h under gentle reflux. The product precipitated and was collected by vacuum filtration followed by washing with cold Et₂O to leave the product as a white solid (7.3 g, 40%) containing trace impurities of PPh₃.

¹H NMR (400 MHz, CDCl₃) δ 8.06 – 7.63 (m, 15H), 7.20 – 7.01 (m, 1H), 3.71 (s, 3H), 1.70 (dd, *J* = 18.4, 6.7 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 134.8, 134.4, 130.3, 116.5, 72.3, 59.7, 15.2 ppm; FT-IR *v*_{max} 524 (s), 537 (s), 689 (s), 724 (m), 996 (m), 1110 (m), 1436 (m).

*(1-Methoxyethyl)triphenylphosphonium tetrafluoroborate*¹²⁵ **263**



Chemical Formula: C₂₁H₂₂BF₄OP

Molecular Weight: 408.18

Triphenylphosphine (5.24 g, 20.0 mmol, 1 equiv.), 1,1-dimethoxyethane (3.2 mL, 30 mmol, 1.5 equiv.) and BF₃.OEt₂ (3.4 mL, 27 mmol, 1.4 equiv.) were stirred in dry toluene (30 mL) at 0 °C for 2 h and then at r.t. for 16 h. The product precipitated during the reaction and was

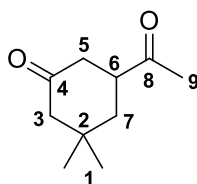
filtered and washed with toluene leaving a white solid (7.65 g, 94%), m.p. 46-48 °C (THF), (lit.47-49 °C).¹²⁵

¹H NMR (400 MHz, CDCl₃) δ 7.89 – 7.65 (m, 15H), 5.79 – 5.65 (m, 1H), 3.58 (s, 3H), 1.67 (dd, *J* = 18.2, 6.7 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 135.2, 134.3 (d, *J* = 9.3 Hz), 130.5 (d, *J* = 11.3 Hz), 116.6 (d, *J* = 82.4 Hz), 72.9 (d, *J* = 69.3 Hz), 59.5 (d, *J* = 11.1 Hz), 14.9 ppm; ³¹P NMR (162 MHz, CDCl₃) δ 23.30 ppm; FT-IR ν_{max} 523 (s), 541 (s), 688 (s), 721 (s), 748 (m), 1047 (s, br), 1440 (m).

General Procedure for the Wittig Reaction with (1-Methoxyethyl)triphenylphosphonium tetrafluoroborate 263

(1-Methoxyethyl)triphenylphosphonium tetrafluoroborate **263** (2.04 g, 5.0 mmol, 1.5 equiv.) was dissolved in dry THF (20 mL) and cooled to -78 °C under N₂. *n*-BuLi (2.5 M in hexane), (2.0 mL, 5 mmol, 1.5 equiv.) was added dropwise *via* syringe to give a deep red solution, this was stirred at -78 °C for 30 min and then for a further 30 min at -40 °C before being re-cooled to -78 °C. A solution of the electrophile (3.33 mmol, 1 equiv.) in dry THF (5 mL) was then added dropwise *via* syringe at -78 °C and the resultant mixture was stirred and allowed to reach r.t. overnight. The reaction was quenched using 1 M HCl (10 mL) and stirred for 1 h at r.t. before the crude mixture was concentrated *in vacuo*. EtOAc (20 mL) was added and the product was extracted with more EtOAc (20 mL). The organic layers were combined, dried over Na₂SO₄ and filtered and then concentrated *in vacuo*. The crude products were purified by SiO₂ column chromatography.

5-Acetyl-3,3-dimethylcyclohexanone 264

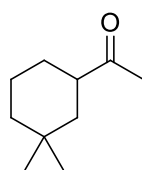


Chemical Formula: C₁₀H₁₆O₂

Molecular Weight: 168.23

Obtained by reaction of salt **263** with 5,5-dimethylcyclohex-2-enone **57** as a colourless liquid (3.33 mmol scale, 254 mg, 45%), isolated by SiO₂ column chromatography (hexane:EtOAc, 8:2), *R_f* (8:2, hexane:EtOAc) 0.2. ¹H NMR (600 MHz, CDCl₃) δ 2.99 – 2.90 (m, 1H, **6**), 2.46 – 2.35 (m, 2H, **5**), 2.21 – 2.18 (d app, 1H, **3**), 2.18 (s, 3H, **9**), 2.11 (dt, *J* = 13.6, 2.2 Hz, 1H, **3**), 1.84 – 1.77 (m, 1H, **7**), 1.58 (t, *J* = 13.1 Hz, 1H, **7**), 1.10 (s, 3H, **1**), 0.93 (s, 3H, **1**) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 210.2 (**4**), 208.4 (**8**), 54.1 (**3**), 47.4 (**6**), 41.6 (**5**), 40.4 (**7**), 35.4 (**2**), 31.8 (**1**), 28.4 (**9**), 25.4 (**1**) ppm; FT-IR *v*_{max} 526 (w), 596 (w), 1168 (w), 1269 (w), 1706 (s), 2957 (w); GC-MS *R_t* 3.67 min, *m/z* 169 [M+H]⁺, 125 [M-Ac]⁺; ASAP-HRMS *m/z* found [M+H]⁺ 169.1225, C₁₀H₁₇O₂ requires 169.1229 (Δ = 2.4 ppm).

1-(3,3-Dimethylcyclohexyl)ethanone¹⁹² 215



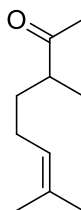
Chemical Formula: C₁₀H₁₈O

Molecular Weight: 154.25

Obtained by reaction of salt **263** with 3,3-dimethylcyclohexanone **58** as a colourless liquid (2.50 mmol scale, 135 mg, 53%), isolated by SiO₂ column chromatography (hexane:EtOAc, 95:5), *R_f* (8:2, hexane:EtOAc) 0.5. ¹H NMR (400 MHz, CDCl₃) δ 2.52 (tt, *J* = 12.4, 3.5 Hz, 1H), 2.15 (s, 3H), 1.88 (m, 1H), 1.70 – 1.35 (m, 4H), 1.25 – 1.07 (m, 3H), 0.96 (s, 3H), 0.93 (s, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 212.6, 47.7, 41.1, 38.6, 33.1, 30.5, 28.2, 28.0,

24.4, 21.6 ppm; FT-IR ν_{\max} 602 (m), 971 (w), 1166 (m), 1188 (m), 1352 (m), 1364 (m), 1461 (m), 1707 (s), 2928 (m); GC-MS R_t 3.12 min, m/z 154 $[M]^+$, 111 $[M-Ac]^+$; ASAP-HRMS m/z found $[M+H]^+$ 155.1432, $C_{10}H_{19}O$ requires 155.1436 ($\Delta = 2.6$ ppm).

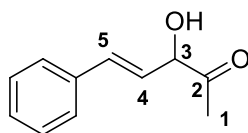
*3,7-Dimethyloct-6-en-2-one*¹⁹³ **267**



Chemical Formula: $C_{10}H_{18}O$
Molecular Weight: 154.25

Obtained by reaction of **263** with 6-methylhept-5-en-2-one as a pale yellow liquid (1.67 mmol scale, 42 mg, 16%), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5), R_f (9:1, hexane:EtOAc) 0.6. 1H NMR (400 MHz, $CDCl_3$) δ 5.10 (m, 1H), 2.54 (m, 1H), 2.15 (s, 3H), 2.04 – 1.94 (m, 2H), 1.75 – 1.54 (m, 6H), 1.46 – 1.33 (m, 2H), 1.11 (d, $J = 7.0$ Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.8, 132.3, 123.7, 46.6, 32.9, 28.0, 25.7, 25.6, 17.7, 16.2 ppm; FT-IR ν_{\max} 541 (s), 695 (s), 743 (m), 1093 (m), 1376 (m), 1436 (m), 1713 (m); GC-MS R_t 3.07 min, m/z 154 $[M]^+$.

(E)-3-Hydroxy-5-phenylpent-4-en-2-one **268**

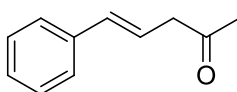


Chemical Formula: $C_{11}H_{12}O_2$
Molecular Weight: 176.21

Obtained by reaction of salt **263** with *trans*-cinnamaldehyde as a yellow liquid (2 mmol scale, 276 mg, 78%), isolated by SiO_2 column chromatography (hexane:EtOAc, 8:2), R_f (8:2, hexane:EtOAc) 0.2. 1H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.26 (m, 5H, ArH), 6.86 (d, $J = 15.8$

Hz, 1H, **5**), 6.15 (dd, $J = 15.8, 7.3$ Hz, 1H, **4**), 4.80 (dd, $J = 7.2, 1.4$ Hz, 1H, **3**), 3.89 (s, br, 1H, OH), 2.30 (s, 3H, **1**) ppm; ^{13}C NMR (176 MHz, CDCl_3) δ 207.0 (**2**), 135.9 (Ar), 134.5 (**5**), 128.7 (Ar), 128.3 (Ar), 126.7 (Ar), 124.9 (**4**), 78.8 (**3**), 25.4 (**1**) ppm; FT-IR ν_{max} 694 (s), 746 (s), 969 (m), 1072 (m), 1120 (m), 1356 (m), 1450 (m), 1604 (m), 1714 (s), 3443 (w, br); GC-MS R_t 4.35 + 4.25 min, m/z 176 $[\text{M}]^+$.

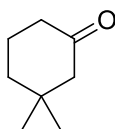
(E)-5-Phenylpent-4-en-2-one¹⁹⁴ **269**



Chemical Formula: $\text{C}_{11}\text{H}_{12}\text{O}$
Molecular Weight: 160.21

Obtained as a side-product by reaction of salt **263** with *trans*-cinnamaldehyde as a colourless liquid (2 mmol scale, 82 mg, 9%), isolated by SiO_2 column chromatography (hexane:EtOAc, 8:2), R_f (8:2, hexane:EtOAc) 0.4. ^1H NMR (400 MHz, CDCl_3) δ 7.45 – 7.22 (m, 5H), 6.50 (d, $J = 15.9$ Hz, 1H), 6.34 (dt, $J = 15.8, 7.1$ Hz, 1H), 3.36 (dd, $J = 7.1, 1.3$ Hz, 2H), 2.24 (s, 3H) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ 206.7, 136.8, 133.8, 128.6, 127.6, 126.3, 121.9, 47.8, 29.6 ppm; FT-IR ν_{max} 701 (s), 742 (m), 973 (m), 1073 (m), 1153 (m), 1360 (m), 1499 (m), 1594 (m), 1666 (m), 1716 (s), 2961 (w), 3026 (w); GC-MS R_t 3.97 min, m/z 160 $[\text{M}]^+$, 117 $[\text{M-Ac}]^+$

3,3-Dimethylcyclohexanone¹⁹⁵ **58**



Chemical Formula: $\text{C}_8\text{H}_{14}\text{O}$
Molecular Weight: 126.20

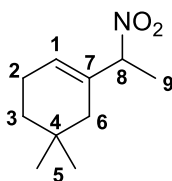
Prepared in-house at IFF *via* selective hydrogenation of dimedone according to the literature.¹⁹⁵ ^1H NMR (400 MHz, CDCl_3) δ 2.31 – 2.25 (m, 2H), 2.16 (t, $J = 0.8$ Hz, 2H), 1.94 – 1.85 (m, 2H), 1.62 – 1.57 (m, 2H), 0.99 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 212.3, 55.0, 40.9, 38.0,

36.1, 28.6, 22.5 ppm; FT-IR ν_{\max} 503 (w), 1076 (w), 1225 (m), 1291 (w), 1368 (w), 1455 (w), 1708 (s), 2954 (m, br); GC-MS R_t 2.60 min, m/z 126 $[M]^+$, 111 $[M-Me]^+$.

General Procedure for the Amine-Catalysed Irregular Nitro-Aldol reaction

A mixture of 3,3-dimethylcyclohexanone (40.0 g, 0.305 mol), *N,N*-diethylethylenediamine (4.3 mL, 10 mol%), EtOAc (30 mL) and nitroethane (214 mL, 10 equiv.) was stirred in a round-bottom flask equipped with Dean-Stark trap (pre-filled with EtOAc) and reflux condenser and heated to 100 °C. After 3 h, a second portion of *N,N*-diethylethylenediamine (4.3 mL, 10 mol%) was added and a third portion (4.3 mL, 10 mol%) was added after a further 3 h. After a total of 22 h the reaction was cooled to r.t. and the nitroethane and EtOAc were removed under reduced pressure. EtOAc (100 mL) was added and amine residues were removed by washing with 1M HCl (2 x 100 mL). The remaining solution was concentrated *in vacuo* to give the crude product which was purified according to the method indicated below.

5,5-Dimethyl-1-(1-nitroethyl)cyclohex-1-ene (α) 277

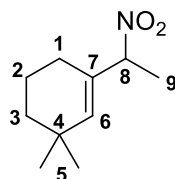


Chemical Formula: $C_{10}H_{17}NO_2$
Molecular Weight: 183.25

Obtained by reaction of nitroethane with 3,3-dimethyl cyclohexanone as a pale yellow liquid (0.305 mol scale, 43.3 g, 78%, $\alpha:\beta = 5.4:1$), isolated by vacuum distillation (b.p. 105-110 °C/10 mbar). 1H NMR (400 MHz, $CDCl_3$) δ 5.90 (m, 1H, **1**), 5.00 (q, $J = 7.6$ Hz, 1H, **8**), 2.14 (m, 2H, **6**), 1.88 – 1.71 (qq, $J = 18.9, 2.0$ Hz, 2H, **2**), 1.62 (d, $J = 6.8$ Hz, 3H, **9**), 1.39 – 1.33 (m, 2H, **3**), 0.93 (s, 3H, **5**), 0.91 (s, 3H, **5**) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.0 (**7**), 128.4 (**1**), 88.3 (**8**), 37.8 (**2**), 34.4 (**3**), 28.8 (**4**), 28.3 (**5**), 27.4 (**5**), 23.2 (**6**), 16.9 (**9**) ppm; FT-IR ν_{\max} 663

(w), 860 (w), 1364 (w), 1384 (m), 1449 (w), 1545 (s), 2918 (w); GC-MS R_t 3.71 min, m/z 137 $[M-NO_2]^+$; ASAP-HRMS m/z found $[M+H]^+$ 184.1344, $C_{10}H_{18}NO_2$ requires 184.1338 ($\Delta = 3.3$ ppm).

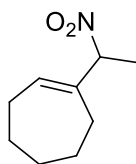
3,3-Dimethyl-1-(1-nitroethyl)cyclohex-1-ene (β) **278**



Chemical Formula: $C_{10}H_{17}NO_2$
Molecular Weight: 183.25

Obtained by reaction of nitroethane with 3,3-dimethyl cyclohexanone as a pale yellow liquid (0.305 mol scale, 43.3 g, 78%, $\alpha:\beta = 5.4:1$), isolated by vacuum distillation (b.p. 105-110 °C/10 mbar). 1H -NMR and ^{13}C -NMR resolved using 2-D techniques on a mixture comprising mostly the α -product **277x**. 1H NMR (600 MHz, $CDCl_3$) δ 5.59 (s, 1H, **6**), 4.92 (q, $J = 7.0$ Hz, 1H, **8**), 2.02 – 1.87 (m, 2H, **1**), 1.67 – 1.62 (m, 2H, **2**), 1.62 (d, $J = 6.8$ Hz, 3H, **9**), 1.45 – 1.35 (m, 2H, **3**), 0.98 (s, 3H, **5**), 0.97 (s, 3H, **5**) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.5 (**6**), 130.8 (**7**), 88.3 (**8**), 36.5 (**3**), 32.0 (**4**), 29.6 (**5**), 29.2 (**5**), 24.3 (**1**), 19.4 (**2**), 17.0 (**9**) ppm; FT-IR ν_{max} 663 (w), 860 (w), 1364 (w), 1384 (m), 1449 (w), 1545 (s), 2918 (w); GC-MS R_t 3.61 min, m/z 137 $[M-NO_2]^+$; ASAP-HRMS m/z found $[M+H]^+$ 184.1344, $C_{10}H_{18}NO_2$ requires 184.1338 ($\Delta = 3.3$ ppm).

*1-(1-Nitroethyl)cyclohept-1-ene*¹²⁸ **295**

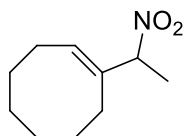


Chemical Formula: C₉H₁₅NO₂

Molecular Weight: 169.22

Obtained by reaction of nitroethane with cycloheptanone as a yellow liquid (50.0 mmol scale, 5.17 g, 61%), isolated by SiO₂ column chromatography (hexane:EtOAc, 95:5), R_f (8:2, hexane:EtOAc) 0.7. ¹H NMR (400 MHz, CDCl₃) δ 6.05 (t, *J* = 6.5 Hz, 1H), 4.99 (q, *J* = 6.9 Hz, 1H), 2.25 – 2.18 (m, 4H), 1.81 – 1.74 (m, 2H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.59 – 1.44 (m, 4H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 139.4, 134.8, 89.5, 32.3, 28.4, 28.3, 26.6, 26.2, 17.3 ppm; FT-IR ν_{max} 861 (m), 1354 (m), 1384 (m), 1447 (m), 1544 (s), 2850 (w), 2921 (m); GC-MS R_t 3.63 min, *m/z* 123 [M-NO₂]⁺.

*1-(1-Nitroethyl)cyclooct-1-ene*¹²⁸ **297**

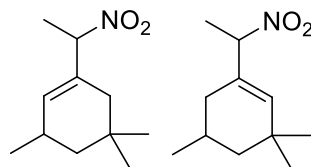


Chemical Formula: C₁₀H₁₇NO₂

Molecular Weight: 183.25

Obtained by reaction of nitroethane with cyclooctanone as a pale yellow liquid (50.0 mmol scale, 3.60 g, 39%), isolated by SiO₂ column chromatography (hexane:EtOAc, 95:5), R_f (9:1, hexane:EtOAc) 0.5. ¹H NMR (400 MHz, CDCl₃) δ 5.90 (t, *J* = 8.2 Hz, 1H), 5.05 (q, *J* = 6.8 Hz, 1H), 2.33 – 2.26 (m, 2H), 2.24 – 2.16 (m, 2H), 1.65 (d, *J* = 6.8 Hz, 3H), 1.60 – 1.42 (m, 8H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 135.6, 132.7, 88.5, 29.4, 29.0, 26.3, 26.3, 26.2, 26.1, 17.6 ppm; FT-IR ν_{max} 758 (w), 860 (w), 1359 (w), 1383 (w), 1449 (w), 1469 (w), 1545 (s), 2852 (w), 2926 (m); GC-MS R_t 4.05 min, *m/z* 137 [M-NO₂]⁺.

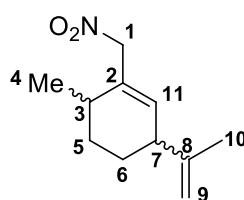
3,5,5-Trimethyl-1-(1-nitroethyl)cyclohex-1-ene/3,3,5-trimethyl-1-(1-nitroethyl)cyclohex-1-ene **299/300**



Chemical Formula: C₁₁H₁₉NO₂
Molecular Weight: 197.27

Obtained by reaction of nitroethane with cyclooctanone as a pale yellow liquid (50.0 mmol scale, 2.51 g, 25%), isolated by SiO₂ column chromatography (hexane:EtOAc, 95:5), R_f (9:1, hexane:EtOAc) 0.4. Obtained as a mixture of *endo* double bond isomers along with the two corresponding *exo* isomers. NMR spectra of mixture not resolved; FT-IR ν_{max} 1362 (m), 1384 (m), 1456 (m), 1520 (s), 1548 (s), 2907 (m), 2952 (m); GC-MS R_t 3.74 + 3.69 min, *m/z* 151 [M-NO₂]⁺; ASAP-HRMS *m/z* found [M+H]⁺ 198.1483, C₁₁H₂₀NO₂ requires 198.1494 (Δ = 5.6 ppm).

6-Methyl-1-(nitromethyl)-3-(prop-1-en-2-yl)cyclohex-1-ene (major product) **306**

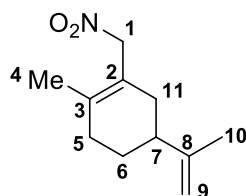


Chemical Formula: C₁₁H₁₇NO₂
Molecular Weight: 195.26

Obtained by reaction of nitromethane with dihydrocarvone as a pale yellow liquid (50.0 mmol scale, 8.65 g, 89%), purified by SiO₂ column chromatography (hexane:EtOAc, 95:5) as a mixture of diastereoisomers along with the double bond isomer, **307** (**306:307** = 3.3:1.0), R_f (8:2, hexane:EtOAc) 0.6. ¹H NMR (700 MHz, CDCl₃) δ 5.80 (s, 1H, **11**), 5.04 – 4.98 (m, 1H, **1**), 4.80 (m, 1H, **9**), 4.79 – 4.74 (m, 1H, **1**), 4.69 (m, 1H, **9**), 2.85 – 2.77 (m, 1H, **7**), 2.33 – 2.27

(m, 1H, **3**), 1.89 – 1.67 (m, 2x1H, **5** + **6**), 1.74 – 1.71 (m, 3H, **10**), 1.59 – 1.42 (m, 1+0.5H, **6** + 0.5(**5**)), 1.32 (m, 0.5H, **5**), 1.06 (dd, $J = 7.1, 3.7$ Hz, 3H, **4**) ppm; ^{13}C NMR (176 MHz, CDCl_3) δ (147.6 + 147.5, **8**), (136.8 + 136.3, **11**), (133.6 + 133.4, **2**), (111.5 + 111.2, **9**), (80.6 + 80.4, **1**), (43.7 + 43.3, **7**), (30.5 + 30.0, **3**), (29.5 + 28.8, **5**), (25.0 + 23.5, **6**), (21.1 + 21.0, **10**), (19.0 + 18.9, **4**) ppm. FT-IR ν_{max} 892 (m), 1372 (m), 1428 (w), 1549 (s), 1644 (w), 2936 (w); GC-MS R_t 3.94 + 3.96 min, m/z 149 $[\text{M}-\text{NO}_2]^+$; ASAP-HRMS m/z found $[\text{M}+\text{H}]^+$ 196.1326, $\text{C}_{11}\text{H}_{18}\text{NO}_2$ requires 196.1338 ($\Delta = 6.1$ ppm).

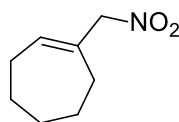
1-Methyl-2-(nitromethyl)-4-(prop-1-en-2-yl)cyclohex-1-ene (minor product) 307



Chemical Formula: $\text{C}_{11}\text{H}_{17}\text{NO}_2$
Molecular Weight: 195.26

Obtained by reaction of nitromethane with dihydrocarvone as a pale yellow liquid (50.0 mmol scale, 8.65 g, 89%), purified by SiO_2 column chromatography (hexane:EtOAc, 95:5) as a mixture of diastereoisomers along with the double bond isomer, **306** (**306:307** = 3.3:1.0), R_f (8:2, hexane:EtOAc) 0.6. ^1H NMR (700 MHz, CDCl_3) δ 4.98 – 4.89 (dd, $J = 41.8, 6.0$ Hz, 2H, **1**), 4.73 (m, 1H, **9**), 4.70 - 4.69 (m, 1H, **9**), 2.22 – 2.02 (m, 5H, **5**, **7**, **11**), 1.81 (m, 1H, **6**), 1.78 (s, 3H, **4**), 1.73 (s, 3H, **10**), 1.46 – 1.42 (m, 1H, **6**) ppm; ^{13}C NMR (176 MHz, CDCl_3) δ 148.8, 138.5, 120.4, 109.1, 78.0, 41.1, 34.0, 32.5, 27.3, 20.7, 19.2 ppm; FT-IR ν_{max} 892 (m), 1372 (m), 1428 (w), 1549 (s), 1644 (w), 2936 (w); GC-MS R_t 4.09 min, m/z 149 $[\text{M}-\text{NO}_2]^+$; ASAP-HRMS m/z found $[\text{M}+\text{H}]^+$ 196.1326, $\text{C}_{11}\text{H}_{18}\text{NO}_2$ requires 196.1338 ($\Delta = 6.1$ ppm).

*1-(Nitromethyl)cyclohept-1-ene*¹²⁸ **305**

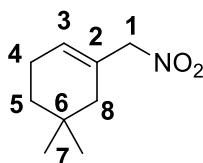


Chemical Formula: C₈H₁₃NO₂

Molecular Weight: 155.19

Obtained by reaction of nitromethane with cycloheptanone as a yellow liquid (50.0 mmol scale, 5.83 g, 75%), isolated by SiO₂ column chromatography (hexane:EtOAc, 95:5), R_f (8:2, hexane:EtOAc) 0.6. ¹H NMR (400 MHz, CDCl₃) δ 6.07 (t, *J* = 6.4 Hz, 1H), 4.84 (d, *J* = 0.8 Hz, 2H), 2.34 – 2.16 (m, 4H), 1.84 – 1.73 (m, 2H), 1.65 – 1.50 (m, 4H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 138.4, 134.4, 84.4, 31.9, 31.3, 28.6, 26.3, 26.2 ppm; FT-IR ν_{max} 643 (m), 848 (w), 1306 (w), 1370 (m), 1447 (w), 1547 (s), 2851 (w), 2923 (m); GC-MS R_t 3.50 min, *m/z* 109 [M-NO₂]⁺.

5,5-Dimethyl-1-(nitromethyl)cyclohex-1-ene **303**

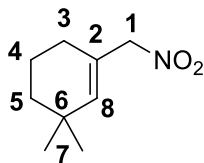


Chemical Formula: C₉H₁₅NO₂

Molecular Weight: 169.22

Obtained by reaction of nitromethane with 3,3-dimethylcyclohexanone as a pale yellow liquid (55.0 mmol scale, 8.80 g, 94%), isolated by SiO₂ column chromatography (hexane:EtOAc, 98:2) as a mixture of double bond isomers (3.0:1, **303:304**), R_f (9:1, hexane:EtOAc) 0.7. ¹H NMR (700 MHz, CDCl₃) δ 5.91 – 5.88 (m, 1H, **3**), 4.79 (s, 2H, **1**), 2.16 – 2.12 (m, 2H, **4**), 1.84 (s, 2H, **8**), 1.34 (t, *J* = 6.4 Hz, 2H, **5**), 0.92 (s, 6H, **7**) ppm; ¹³C NMR (176 MHz, CDCl₃) δ 132.0 (**3**), 127.4 (**2**), 82.7 (**1**), 40.3 (**8**), 34.2 (**5**), 29.0 (**6**), 27.9 (**7**), 23.3 (**4**) ppm; FT-IR ν_{max} 665 (w), 1367 (m), 1428 (w), 1550 (s), 2920 (w, br); GC-MS R_t 3.42 min, *m/z* 123 [M-NO₂]⁺; ASAP-HRMS *m/z* found [M+H]⁺ 170.1186, C₉H₁₆NO₂ requires 170.1181 (Δ = 2.9 ppm).

3,3-Dimethyl-1-(nitromethyl)cyclohex-1-ene **304**



Chemical Formula: C₉H₁₅NO₂

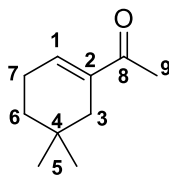
Molecular Weight: 169.22

Obtained by reaction of nitromethane with 3,3-dimethylcyclohexanone as a pale yellow liquid (55.0 mmol scale, 8.80 g, 94%), isolated by SiO₂ column chromatography (hexane:EtOAc, 98:2) as a mixture of double bond isomers (3.0:1, **303:304**), R_f (9:1, hexane:EtOAc) 0.7. ¹H NMR (700 MHz, CDCl₃) δ 5.64 – 5.61 (m, 1H, **8**), 4.77 (s, 2H, **1**), 2.01 (t, *J* = 6.3 Hz, 2H, **3**), 1.70 – 1.65 (m, 2H, **4**), 1.43 – 1.40 (m, 2H, **5**), 1.00 (s, 6H, **7**) ppm; ¹³C NMR (176 MHz, CDCl₃) δ 143.0 (**8**), 126.2 (**2**), 82.8 (**1**), 36.2 (**5**), 32.3 (**6**), 29.3 (**7**), 26.6 (**3**), 19.3 (**4**) ppm; FT-IR ν_{max} 665 (w), 1367 (m), 1428 (w), 1550 (s), 2920 (w, br); GC-MS R_t 3.37 min, *m/z* 123 [M-NO₂]⁺; ASAP-HRMS *m/z* found [M+H]⁺ 170.1186, C₉H₁₆NO₂ requires 170.1181 (Δ = 2.9 ppm).

General Procedure for the Nef Reaction of Nitro Olefins

The nitro olefin (15.0 g, 82.0 mmol) was dissolved in EtOH (140 mL) and NaOH (4.10 g, 1.25 equiv.) was added, the mixture was stirred at r.t. for 30 min after which time the nitronate salt had precipitated. The suspension was cooled to 0 °C and a solution of H₂SO₄ (8.75 mL, 2 equiv.) in H₂O (41 mL) was added. After 1 h of stirring at 0 °C the reaction was allowed to warm to r.t. and stirred for a further 2 h. The EtOH was then removed under reduced pressure and the residue was neutralised with aqueous NaOH. The product was then extracted with DCM (3 x 60 mL) and the combined organic layers were concentrated under reduced pressure. Pure product was obtained according to the indicated method.

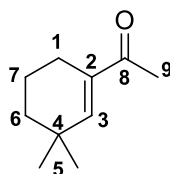
1-(5,5-Dimethylcyclohex-1-en-1-yl)ethanone (α) **65**



Chemical Formula: C₁₀H₁₆O
Molecular Weight: 152.23

Obtained from **277/278** (82.0 mmol scale, 8.11 g, 65%, $\alpha:\beta = 5.4:1$), isolated by vacuum distillation (b.p. 85 - 95 °C/9 mbar). ¹H and ¹³C NMR spectra of α/β -mixture resolved by 2-D NMR experiments (COSY, HMBC, HSQC) and Pureshift ¹H NMR. ¹H NMR (700 MHz, CDCl₃) δ 6.87 (m, 1H, **1**), 2.28 (m(obsured), 2H, **7**), 2.28 (s, 3H, **9**), 2.01 (q, $J = 2.2$ Hz, 2H, **3**), 1.34 (t, $J = 6.4$ Hz, 2H, **6**), 0.90 (s, 6H, **5**) ppm; ¹³C NMR (176 MHz, CDCl₃) δ 199.5 (**8**), 139.7 (**1**), 138.7 (**2**), 36.4 (**3**), 34.2 (**6**), 28.5 (**4**), 28.0 (**5**), 25.3 (**9**), 24.1 (**7**) ppm; GC-MS R_t 3.32 min, m/z 152 [M]⁺, 109 [M-Ac]⁺; ASAP-HRMS m/z found [M+H]⁺ 153.1281, C₁₀H₁₇O requires 153.1279 ($\Delta = 1.3$ ppm).

1-(3,3-Dimethylcyclohex-1-en-1-yl)ethanone (β) **66**

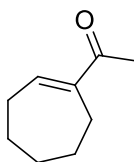


Chemical Formula: C₁₀H₁₆O
Molecular Weight: 152.23

Obtained from **277/278** (82.0 mmol scale, 8.11 g, 65%, $\alpha:\beta = 5.4:1$), isolated by vacuum distillation (b.p. 85 - 95 °C/9 mbar). ¹H and ¹³C NMR spectra of α/β -mixture resolved by 2-D NMR experiments (COSY, HMBC, HSQC) and Pureshift ¹H NMR. ¹H NMR (700 MHz, CDCl₃) δ 6.53 (t, $J = 1.7$ Hz, 1H, **3**), 2.27 (s, 3H, **9**), 2.15 (td, $J = 6.3, 1.7$ Hz, 2H, **1**), 1.61 (m, 2H, **7**), 1.43 (m, 2H, **6**), 1.06 (s, 6H, **5**) ppm; ¹³C NMR (176 MHz, CDCl₃) δ 199.9 (**8**), 149.7

(**3**), 137.3 (**2**), 36.3 (**6**), 32.7 (**4**), 29.1 (**5**), 25.2 (**9**), 23.1 (**1**), 19.1 (**7**) ppm; GC-MS R_t 3.24 min, m/z 152 $[M]^+$, 109 $[M-Ac]^+$; ASAP-HRMS m/z found $[M+H]^+$ 153.1281, $C_{10}H_{17}O$ requires 153.1279 ($\Delta = 1.3$ ppm).

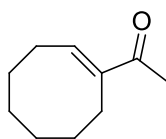
*1-(Cyclohept-1-en-1-yl)ethanone*¹⁹⁶ **308**



Chemical Formula: $C_9H_{14}O$
Molecular Weight: 138.21

Obtained from **295** as a colourless liquid (10.0 mmol scale, 584 mg, 42%), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5), R_f (8:2, hexane:EtOAc) 0.4. 1H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, $J = 6.7$ Hz, 1H), 2.50 – 2.45 (m, 2H), 2.37 – 2.30 (m, 2H), 2.28 (s, 3H), 1.80 – 1.73 (m, 2H), 1.58 – 1.51 (m, 2H), 1.47 – 1.40 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 146.5, 145.5, 32.2, 29.1, 26.1, 25.8, 25.3, 25.2 ppm; FT-IR ν_{max} 857 (m), 985 (m), 1198 (m), 1252 (m), 1280 (m), 1350 (m), 1449 (m), 1662 (s), 2850 (m), 2919 (m); GC-MS R_t 3.18 min, m/z 138 $[M]^+$, 95 $[M-Ac]^+$.

*1-(Cyclooct-1-en-1-yl)ethanone*¹⁹⁷ **309**

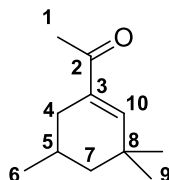


Chemical Formula: $C_{10}H_{16}O$
Molecular Weight: 152.23

Obtained from **297** as a colourless liquid (5.80 mmol scale, 417 mg, 47%), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5), R_f (8:2, hexane:EtOAc) 0.4. 1H NMR (400 MHz, $CDCl_3$) δ 6.89 (t, $J = 8.3$ Hz, 1H), 2.49 – 2.44 (m, 2H), 2.39 – 2.33 (m, 2H), 2.33 (s, 3H), 1.69 – 1.62 (m, 2H), 1.59 – 1.41 (m, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 143.5, 143.1, 29.2, 29.1, 27.5, 26.5, 26.1, 25.4, 23.4 ppm; FT-IR ν_{max} 755 (m), 1199 (m), 1284 (m),

1350 (w), 1383 (w), 1653 (m), 1662 (s), 2852 (m), 2922 (m); GC-MS R_t 3.58 min, m/z 152 $[M]^+$.

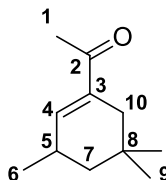
1-(3,3,5-Trimethylcyclohex-1-en-1-yl)ethanone **310**



Chemical Formula: $C_{11}H_{18}O$
Molecular Weight: 166.26

Mixture of **310** and **311** obtained from **299/300** as a colourless liquid (9.29 mmol scale, 695 mg, 54%, **311:310** = 1.9:1), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5), R_f (8:2, hexane:EtOAc) 0.6. 1H NMR (600 MHz, $CDCl_3$) δ 6.52 (m, 1H, **10**), 2.50 – 2.44 (m, 1H, **4**), 2.27 (s, 3H, **1**), 1.71 – 1.63 (m, 1H, **5**), 1.56 – 1.51 (m, 1H, **4**), 1.51 – 1.48 (m, 1H, **7**), 1.07 (s, 3H, **9**), 1.05 (s, 3H, **9**), 1.02 (m, 1H, **7**), 0.99 (d, J = 6.6 Hz, 3H, **6**) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.8 (**2**), 149.5 (**10**), 137.0 (**3**), 45.3 (**7**), 34.1 (**8**), 31.8 (**4**), 30.4 (**9**), 28.4 (**9**), 25.6 (**5**), 25.3 (**1**), 22.0 (**6**) ppm; FT-IR ν_{max} (mixture) 755 (m), 1248 (m), 1364 (w), 1456 (w), 1635 (m), 1665 (s), 2870 (w), 2954 (m); GC-MS R_t 3.13 min, m/z 166 $[M]^+$; ASAP-HRMS m/z found $[M+H]^+$ 167.1425, $C_{11}H_{19}O$ requires 167.1436 (Δ = 6.6 ppm).

1-(3,5,5-Trimethylcyclohex-1-en-1-yl)ethanone **311**

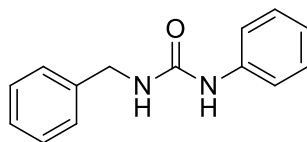


Chemical Formula: $C_{11}H_{18}O$
Molecular Weight: 166.26

Mixture of **310** and **311** obtained from **299/300** as a colourless liquid (9.29 mmol scale, 695 mg, 54%, **311:310** = 1.9:1), isolated by SiO_2 column chromatography (hexane:EtOAc, 95:5),

R_f (8:2, hexane:EtOAc) 0.6. ¹H NMR (600 MHz, CDCl₃) δ 6.66 (m, 1H, **4**), 2.44 – 2.38 (m, 1H, **5**), 2.29 (s, 3H, **1**), 2.19 – 2.13 (m, 1H, **10**), 1.84 – 1.78 (m, 1H, **10**), 1.50 – 1.45 (m, 1H, **7**), 1.09 (d, *J* = 7.2 Hz, 3H, **6**), 1.00 (s, 3H, **9**), 0.97 – 0.92 (m, 1H, **7**), 0.80 (s, 3H, **9**) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 199.8 (**2**), 144.9 (**4**), 137.8 (**3**), 43.9 (**7**), 36.5 (**10**), 31.7 (**9**), 29.5 (**8**), 29.5 (**5**), 25.4 (**1**), 25.1 (**9**), 20.7 (**6**) ppm; FT-IR ν_{max} (mixture) 755 (m), 1248 (m), 1364 (w), 1456 (w), 1635 (m), 1665 (s), 2870 (w), 2954 (m); GC-MS R_t 3.34 min, *m/z* 166 [M]⁺; ASAP-HRMS *m/z* found [M+H]⁺ 167.1425, C₁₁H₁₉O requires 167.1436 (Δ = 6.6 ppm).

l-Benzyl-3-phenylurea¹⁹⁸ **324**



Chemical Formula: C₁₄H₁₄N₂O

Molecular Weight: 226.27

Prepared according to the literature.¹⁹⁸ ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.55 (s, 1H), 7.44 – 7.19 (m, 9H), 6.90 (tt, *J* = 7.3, 1.2 Hz, 1H), 6.60 (t, *J* = 6.0 Hz, 1H), 4.30 (d, *J* = 5.9 Hz, 2H) ppm; ¹³C NMR (101 MHz, DMSO-*d*₆) δ 155.7, 140.9, 140.8, 129.1, 128.8, 127.6, 127.2, 121.6, 118.1, 43.2 ppm; FT-IR ν_{max} 499 (m), 695 (s), 758 (m), 1220 (m), 1310 (m), 1542 (s), 1598 (m), 1685 (w), 3302 (w, br); GC-MS R_t 5.84 min, *m/z* 226 [M]⁺, 93 [H₂NPh]⁺.

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